MATERIAL TIRC

for

SCIENTIFIC ADVISORY BOARD MEETING

MAY 26 - 27, 1962

10035428847

Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000

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AGENDA

SCIENTIFIC ADVISORY BOARD

May 26-27, 1962

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1. Administrative actions taken since March 9-10-11, 1962. (For confirmation.)

2. Applications
   (a) Renewals
   (b) New Applications

3. Program planning
   (a) Conferences and symposia
       Reports and plans.
   (b) Psychophysiological research
   (c) Inhalation practices
   (d) Staff recommendations
   (e) Other suggestions

4. Miscellaneous

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CONFIDENTIAL REPORT

SCIENTIFIC ADVISORY BOARD MEETING

Fort Lauderdale, Florida

March 9-10-11, 1962

Attendance

Dr. Kenneth M. Lynch, Chairman	
Dr. C. C. Little	Scientific Director, TIRC
Dr. Richard J. Bing	
Dr. McKeen Cattell	
Dr. Leon O. Jacobson	
Dr. Paul Kotin	
Dr. Stanley P. Reimann	
Dr. Edwin B. Wilson	
Dr. H. B. Parmele	Chairman, ITC
Mr. T. V. Hartnett	Chairman, TIRC
Mr. W. T. Hoyt	Executive Director, TIRC
Dr. Robert C. Hockett	Associate Scientific Director, TIRC
Dr. J. Morrison Brady	Associate Scientific Director, TIRC
Mr. Carl Thompson	Hill and Knowlton, Inc.

1. The report of actions taken at the last meeting was approved by the Board.

2. This being the annual meeting of the Advisory Board, upon a motion made and seconded, Drs. Kotin, Lynch and Wilson were re-elected to the Board for 3-year terms. Dr. Lynch was also re-elected Chairman.

3. Administrative Actions

#134AR5-Supp. - George O. Gey, M.D. A supplementary grant in the amount of $10,810.00 was approved.

#243R1 - Lawrence L. Hester Jr., M.D. Time extension from February 1 to April 1, 1962 was authorized without additional funds.

#264 - Robert H. Linnell, Ph.D. The University of Vermont was permitted to retain the balance on hand, $779.15, for the use of the Chemistry Department.

#275R1 - Caroline Bedell Thomas, M.D. A time extension of one year to August 31, 1963 was granted to use the balance of funds on hand.

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#283R1 - Ebbe Curtis Hoff, Ph.D., M.D. A transfer in budget category (from Salaries to Permanent Equipment) of $3,500.00 was approved to purchase a fluoroscopic x-ray unit.

#288 - Hobart A. Reimann, M.D. Residual funds, whatever they may be, were authorized to be retained and used for an extension of the project until they are exhausted.

#291 - Hans L. Falk, Ph.D. A time extension was granted with no additional funds from February 1 to June 30, 1962.

#331 - E. P. Toman, Ph.D. This application, which had been approved in principle at the December meeting in the amount of $9,900.00 was formally approved following better definition of objectives.

4. Renewal Applications

#24R6 - Paul S. Larson, Ph.D. $9,251.00 Approved.

#80R7 - 1962 Fellowship Program. Approved in an amount equal to that of 1961, $40,600.00, with such minor flexibility as is required by the staff.

#170R4 - Edward W. Pelikan, M.D. $13,100.88 Approved.

#180R4 - Frederic A. French, A.B. $5,750.00 Approved.

#223R3 - Herbert McKennis Jr., Ph.D. $39,784.00 Approved.

#252R2 - Otakar J. Pollak, M.D., Ph.D. $13,480.00 Denied in line with his having been advised that the last grant was terminal. Any future grants will depend upon further discussions.

#258AR2 - Ralph S. Becker, Ph.D. $11,410.00 Approved.

#276R2 - Forde A. McIver, M.D. $9,688.00 Approved.

#293R1 - Shields Warren, M.D. $1,500.00 Approved.

#294R1 - Jay D. Coffman, M.D. $3,240.00 Approved. Terminal.

#298R1 - Stephen M. Ayres, M.D. $6,808.00 Approved.

#302R1 - J. P. Long, Ph.D. $7,231.00 Approved.

#305R1 - Robert W. Hull, Ph.D. $8,507.50 Approved conditionally pending receipt of full report and data for first year.

#307R1 - Samuel Bellet, M.D. $11,930.00 Approved.

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#310R1 - Richard J. Bing, M.D. $10,435.68 Approved.

#312R1 - Cecilie Leuchtenberger, Ph.D. $14,188.13 Approved for six months for completing study of material on hand. New studies are not to be supported in Zurich. Terminal.

#320R1 - Peter F. Salisbury, M.D., Ph.D. $13,225.00 Approved.

5. New Applications

#334 - Herman R. Haymond, Ph.D. $13,800.00 Approved, subject to receipt of a new application satisfactory to Drs. Wilson and Kotin.

#336 - Ernest Sondheimer, Ph.D. $8,625.00 Approved.

#337 - Robert P. McCombs, M.D. $4,900.00 Denied.

#338 - Freddy Homburger, M.D. $31,532.00 Approved in an amount not to exceed the sum cited in the application request. Dr. Little was asked to discuss a revision in the application with Dr. Homburger, which revision must be subject to the approval of Drs. Little, Jacobson and Kotin.

#339 - E. T. Angelakos, M.D., Ph.D. $16,922.00 total for two years. Postponed until the May meeting, pending investigation of the project by Drs. Bing and Hockett.

#340 - C. Harold Steffee, M.D. $37,672.00 total for two years. Approved tentatively, subject to a reorientation of the application by a subcommittee consisting of Drs. Kotin, Jacobson and Little.

#341 - Thomas M. Gocke, M.D. $11,902.50 Approved.

6. Dr. Hockett reported that he had invited Dr. Renato Dulbecco to attend the SAB meeting but he had been unable to do so.

7. Dr. Reimann discussed at length the forthcoming cell differentiation conference, which will be held on April 21, 1962, and requested the staff to send a reminder note to the Board concerning attendance by individual members.

8. Dr. Brady reported on the 1961 Fellowship Program. Ninety-one fellowships were offered: 11 in the amount of $600.00 and 80 at $500.00, totaling $46,600.00. Of these, 81 were accepted and paid: 10 at $600.00 and 71 at $500.00, amounting to $41,500.00, less a refund of $111.08. The total expenditure, therefore, for the 1961 Fellowship Program to date is $41,388.92.

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9. Plans and Programs J. Bing, M.D., S.D., Approved

A lengthy discussion on planning and programming of research took place. The Scientific Director and his staff were asked to consolidate the discussion for presentation at the May meeting.

10. The Board suggested that the staff draw up a letter to medical and graduate schools advising of the TIRC research program, and a subcommittee, composed of Drs. Bing, Jacobson and Lynch, was appointed to review it before mailing.

11. Meeting dates were established for the remainder of 1962 as follows:

May 26-27
September 29-30
December 8-9

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APPLICATIONS TO BE CONSIDERED

May 26-27, 1962

Grant #	Principal Investigator	Amount Requested	Last Grant	Category	Subcommittee
RENEWALS					
194R3 (Supp.)	Pace	1,890.00	11,575.00	Tissue Culture	Little, Lynch, Reimann
278R2	Montgomery	17,392.00	15,780.00	Carcinogenesis	Reimann, Kotin, Jacobson
321R1	Kuhn	28,420.00	10,350.00	Cardiovascular	Jacobson, Bing, Cattell
DEFERRED					
339	Angelakos	8,461.00		Cardiovascular	Bing, Cattell, Jacobson
NEW					
342	Stowens	13,725.00		Pathologic	Kotin, Lynch, Reimann
343	Protzel	21,781.05		Carcinogenesis	Jacobson, Kotin, Wilson
344	Redisch	6,654.00		Cardiovascular	Bing, Cattell, Wilson
345	Wenzel	8,795.00		Pharmacology	Cattell, Jacobson, Wilson
346	Albanese	7,590.00		Chemistry	Wilson, Jacobson, Cattell
347	Kaplan	13,092.00		Psychosomatic	Wilson, Cattell, Jacobson, Little
348	Clark	17,824.25		Pharmacology	Jacobson, Cattell Bing
349	Furst	7,360.00		Bioassay	Kotin, Jacobson, Reimann, (Little)
350	Mahlberg	9,545.00		Miscellaneous	Jacobson, Lynch, Cattell, (Parmele)
351	Wender	15,810.00		Chemistry	Jacobson, Kotin, Cattell
352	Tuttle	9,993.00		Pathologic	Reimann, Lynch, Rienhoff, Kotin
353	LaBelle	7,015.00		Lung Physiology	Cattell, Kotin, Jacobson, Rienhoff
354	Katz	2,587.50		Psychosomatic	Wilson, Cattell, Little, (Tagiuri)

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APPLICATIONS BY CATEGORY

May 26-27, 1962

			Anniversary	Amount
BIOASSAY, CARCINOGENESIS & TISSUE CULTURE				
Bioassay				
349	-	Furst		7,360.00
Carcinogenesis				
278R2	-	Montgomery, P.O'B.	9/1/62	17,392.00
343	-	Protzel		21,781.05
Tissue Culture				
194R3	-	Pace	2/1/62	1,890.00
CARDIOVASCULAR, PHARMACOLOGY & CHEMISTRY				
Cardiovascular				
321R1	-	Kuhn	8/1/62	28,420.00
339	-	Angelakos		14,976.00(2 yrs.)
344	-	Redisch	5/1/62	21,422.00(3 yrs.)
Pharmacology				
345	-	Wenzel	6/1/62	8,795.00
348	-	Clark	7/1/62	17,824.25
Chemistry				
346	-	Albanese		7,590.00
351	-	Wender		15,810.00
EPIDEMIOLOGY, PSYCHOSOMATIC & STATISTICS				
Psychosomatic				
347	-	Kaplan		33,539.00(3 yrs.)
354	-	Katz		2,587.50
LUNG PHYSIOLOGY				
353	-	LaBelle		7,015.00
PATHOLOGIC-DIAGNOSTIC				
Pathologic				
342	-	Stowens		13,725.00
352	-	Tuttle		9,993.00
MISCELLANEOUS				
350	-	Mahlberg	9/1/62	9,545.00

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TOBACCO INDUSTRY RESEARCH COMMITTEE

May 26-27, 1962

CURRENT GRANTS

(By Subject)

BIOASSAY, CARCINOGENESIS & TISSUE CULTURE

		Activated	Amount	Percent of Total Awards
Bioassay				
180	- F. F. French	1/1/62	5,750.00	
230	- H. R. Pratt-Thomas	2/1/62	7,390.00	
305	- R. W. Hull	4/1/62	8,507.00	
338	- F. Homburger	-	31,532.00	
340	- C. H. Steffee	-	37,672.00	
			90,851.00	15%
Carcinogenesis				
212	- F. Homburger	10/1/61	28,760.00	
258A	- R. S. Becker	4/1/62	11,410.00	
278	- P. O'B. Montgomery Jr.	9/1/61	15,780.00	
290	- W. S. Murray	12/1/61	28,149.00	
293	- S. Warren	2/1/62	1,500.00	
312	- C. Leuchtenberger	6/1/62	14,188.00	
			99,787.00	16%
Tissue Culture				
134A	- G. O. Gey	2/1/62	30,810.00	
194	- D. M. Pace	2/1/62	11,575.00	
			42,385.00	7%
			$233,023.00	38%

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CARDIOVASCULAR, PHARMACOLOGY & CHEMISTRY

CURRENT GRANTS

		Activated	Amount	Percent of Total Awards
Cardiovascular				
246	- C. M. Agress	12/15/61	8,050.00	
275	- C. B. Thomas	9/1/61	5,760.00	
281M	- E. O. Lindseth	11/15/61	27,405.00	
294	- J. D. Coffman	7/1/61	3,240.00	
302	- J. P. Long	6/1/62	7,231.00	
307	- S. Bellet	7/1/62	11,930.00	
310	- R. J. Bing	7/1/62	10,435.00	
320	- P. F. Salisbury	7/1/62	13,225.00	
321	- R. A. Kuhn	8/1/61	10,350.00	
326	- I. Gore	1/1/62	12,000.00	
			109,626.00	18%
Pharmacology				
170	- E. W. Pelikan	4/1/62	13,100.00	
206	- E. F. Domino	1/1/62	9,660.00	
283	- E. C. Hoff	1/1/62	15,000.00	
286	- P. S. Larson	11/15/61	2,970.00	
			40,730.00	7%
Chemistry				
223	- H. S. McKennis	7/1/62	39,784.00	
249	- Sr. M. E. Cahill	8/1/61	3,832.00	
273	- R. U. Byerrum	10/1/61	8,434.00	
336	- E. Sondheimer	7/1/62	8,625.00	
			60,675.00	10%
			$211,031.00	35%

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Current Grants
(By Subject)

EPIDEMIOLOGY, PSYCHOSOMATIC & STATISTICS

		Activated	Amount	Percent of Total Awards
Epidemiology				
276	- F. A. McIver	6/1/62	9,688.00	
334	- H. R. Haymond	5/1/62	13,800.00	
341	- T. M. Gocke	5/1/62	11,902.00	
			35,390.00	6%
	- P. F. Salisbury	7/1/62	13,225.00	
Psychosomatic				
322	- R. Tagiuri	2/1/62	2,000.00	
324	- R. J. Williams	8/1/61	18,900.00	
331	- J. E. P. Toman	2/1/62	9,900.00	
			30,800.00	5%
			$66,190.00	11%

LUNG PHYSIOLOGY

298	- S. M. Ayres	7/1/62	$6,808.00	1%

PATHOLOGICAL, DIAGNOSTIC

174	- J. P. Strong	2/1/62	$14,989.00	2%

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Current Grants
(By Subject)

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VIRUS, PREVIOUS INFECTIONS

		Activated	Amount	Percent of Total Awards
Virus				
327	- P. Cooper	1/1/62	15,070.00	3%
Previous Infections				
265M2	- G. A. Laurenzi	11/1/61	9,474.00	2%
			$24,544.00	5%
MISCELLANEOUS				
24	- P. S. Larson	7/1/61	9,251.00	
80	- Fellowship Program	6/1/61	40,600.00	
			$49,851.00	8%
			$606,436.00	100%

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CURRENT GRANTS

(By Date of Activation)

No.	Grantee	Date	1962	1963
180	F. F. French	1/1	5,750.00	
206	E. F. Domino	"	9,660.00	
283	E. C. Hoff	"	15,000.00	
326	I. Gore	"	12,000.00	
327	P. Cooper	"	15,070.00	
134A	G. O. Gey	2/1	30,810.00	
174	J. P. Strong	"	14,989.00	
194	D. M. Pace	"	11,575.00	
230	H. R. Pratt-Thomas	"	7,390.00	
293	S. Warren	"	1,500.00	
322	R. Tagiuri	"	2,000.00	
331	J. E. P. Toman	"	9,900.00	
			$135,644.00	

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Current Grants
(By Date of Activation)

No.	Grantee	Date	1962	1963
170	E. W. Pelikan	4/1	13,100.00	
258A	R. S. Becker	"	11,410.00	
305	R. W. Hull	"	8,507.00	
334	H. R. Haymond	5/1	13,800.00	
341	T. M. Gocke	"	11,902.00	
80	Fellowship Program	6/1	40,600.00	
276	F. A. McIver	"	9,688.00	
302	J. P. Long	"	7,231.00	
312	C. Leuchtenberger	"	14,188.00	
			$130,426.00	

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Current Grants
(By Date of Activation)

No.	Grantee	Date	1961	1962
24	P. S. Larson	7/1		9,251.00
223	H. McKennis Jr.	"		39,784.00
294	J. D. Coffman	"		3,240.00
298	S. M. Ayres	"		6,808.00
307	S. Bellet	"		11,930.00
310	R. J. Bing	"		10,435.00
320	P. F. Salisbury	"		13,225.00
336	E. Sondheimer	"		8,625.00
338	F. Homburger	?		31,532.00
340	C. H. Steffee	?		37,672.00
249	Sr. M. E. Cahill	8/1	3,832.00	
321	R. A. Kuhn	"	10,350.00	
324	R. J. Williams	"	18,900.00	
275	C. B. Thomas	9/1	5,760.00	
278	P. O'B. Montgomery Jr.	"	15,780.00	
			$54,622.00	$172,502.00

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Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000

Current Grants
(By Date of Activation)

No.	Grantee	Date	1961	1962
212	F. Homburger	10/1	28,760.00	
273	R. U. Byerrum	"	8,434.00	
265M2	G. A. Laurenzi	11/1	9,474.00	
286	P. S. Larson	"	2,970.00	
281M	E. O. Lindseth	11/15	27,405.00	
290	W. S. Murray	12/1	28,149.00	
246	C. M. Agressu	12/15	8,050.00	
			$113,242.00	

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BIOASSAY, CARCINOGENESIS AND TISSUE CULTURE #194R3(Suppl)

COMMITTEE:
Dr. Little, Chm.
Dr. Lynch
Dr. Reimann

Activated: 11/1/58
Renewed: 11/1/59
Extended to 2/1/61
Renewed: 2/1/61

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

APPLICATION FOR RESEARCH GRANT

Date: April 30, 1962

1003542864

1. Name of Investigator: DONALD M. PACE, PH.D.

2. Title: Professor of Physiology

3. Institution & Address: University of Nebraska
Lincoln, Nebraska

4. Project or Subject: To investigate tolerance phenomena in cells (human lung, skin, Strain L, liver).

5. Detailed Plan of Procedure: In general, procedures similar to those used in previous investigations will be followed. However, in those experiments in which the cells will be exposed to gases, use will be made of a modified T-60 flask as described and illustrated in an article by Pace, Thompson, Aftonomos, and Holck (Canadian Jour. Biochem. & Physiol. 39: 1247 (1961). Several copies of this report are enclosed.

We have already made some preliminary observations which suggest the possibility of tolerance in human lung cells similar to that which has been observed in the intact animal. We are continuing this work but will need extra help during the summer months.

Cells will be exposed to low concentrations of various gases and other substances (concentrations that permit survival with little or no injury). At a subsequent time these same cells will be challenged with what would otherwise be lethal concentrations, to determine whether or not true tolerance is developed in isolated cells.

Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000

6. Budget Plan:

a. Salaries	$1,600.00
b. Expendable Supplies	---
c. Permanent Equipment	---
d. Overhead (15% of a,b,e)	240.00
e. Other (Social Security)	50.00
TOTAL	$1,890.00

7. Anticipated Duration of Work: SUMMER 1962

8. Facilities and Staff Available:

This request is supplementary to that already granted for 1962 and the same facilities and staff, other than the person to be hired, are available.

9. Additional Requirements: NONE

10. Additional information (including relation of work to other projects and other sources of supply):

This work will be carried out in close relation to that already underway. In fact, our approach and where we begin that approach is dependent upon what we have already done or are doing in regards to smoke constituents.

Signed DONALD M. PACE
Director of Project

HERB. M. POTTER
University of Nebraska Foundation
Assistant Treasurer

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BIOASSAY, CARCINOGENESIS and TISSUE CULTURE

#278 R2
Activated: 9/1/60
Renewed: 9/1/61

COMMITTEE:
Dr. Reimann, Chm.
Dr. Kotin
Dr. Jacobson

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

APPLICATION FOR RESEARCH GRANT

Date: MAY 3, 1962

1. Name of Investigator: P. O'B. MONTGOMERY, Jr., M.D.
ROLLAND C. REYNOLDS, M. D.

2. Title: Professor of Pathology
Assistant Professor of Pathology

3. Institution & Address: The University of Texas Southwestern Medical School
5323 Harry Hines Boulevard
Dallas 35, Texas

4. Project or Subject: "INVESTIGATION OF NUCLEOLAR CHANGES PRODUCED BY CHEMICAL CARCINOGENS"

5. Detailed Plan of Procedure:

For the past year we have been studying the in-vivo effects of the carcinogenic agent 4-Nitroquinoline N-Oxide on Chang liver cells in tissue culture. Our studies have demonstrated hitherto undescribed morphologic changes in these cells when they are treated with a 10^{-5} Molar concentration of the 4-Nitroquinoline N-Oxide.(1) The most striking of these changes involves the nucleolus. Listed in a sequential fashion these changes are as follows: 1) A progressive decrease in the size of the nucleoli. 2)Occasional fusion of nucleoli (we believe this phenomenon is related to the same factors which produce the progressive decrease in nucleolar size). 3) Finally, the most striking morphologic alteration in the nucleoli consists of a separation of the pars amorpha and the nucleolemma. These changes have been demonstrated by means of electron microscopy and phase time-lapse motion picture studies. The separation of the nucleolemma and pars amorpha results in a characteristic margination of the nucleolemma to produce "caplike" structures at the edges of the nucleoli. As the separation continues the nucleolemmal material migrates to one side of the nucleolus leaving a small "bubble-like" cap of clear pars amorpha at the opposite side of the nucleolus. A small amount of nucleolemmal material is seen covering the protruding pars amorpha. These changes are morphologically quite distinct and may be found in the majority of cells which survive 4-6 hours after treatment with the carcinogen. Other morphologic changes which we have noted in treated Chang liver cells are a slight enlargement of the nuclei, condensation

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of cytoplasmic granules around the Golgi apparatus, and the subsequent development of a clear glassy-like cytoplasm in the surrounding area. The mitochondria appear to remain intact as long as the cells remain alive. The nucleolar changes just described take on increasing significance when one considers other known facts concerning the effects of 4-Nitroquinoline N-Oxide on living cells. These effects have been studied chiefly by Japanese workers who have described the following characteristics of 4-Nitroquinoline N-Oxide:(2) 1) Marked carcinogenic activity. Skin painting of the chemical produces papillomas and squamous cell carcinomas in the mouse. Subcutaneous injection results in sarcomas and an increased incidence of pulmonary tumors in the same animal. 2) The chemical displays a marked avidity for nucleophilic compounds particularly compounds having S-H groups. With S-H containing compounds the drug undergoes a substitution reaction which proceeds at physiologic pH ranges without necessity of enzymatic catalysis. 3) 4-Nitroquinoline N-Oxide is a potent inhibitor of glycolysis and produces a decreased concentration of ATP in cells. 4) Uptake of P^{32} into nucleic acids and of C^{14} labeled amino acids into protein is inhibited. 5) Intranuclear inclusions have been demonstrated when Chang liver cells in tissue culture are treated with 10^{-5} Molar concentrations of the drug and subsequently stained with hematoxylin and Eosin.

CURRENT PROJECT:

The initial goal of our present studies is the correlation of nucleolar changes produced by 4-Nitroquinoline N-Oxide with changes produced by other carcinogenic chemicals. We propose to investigate other major types of carcinogens for the ability to produce the unique "nucleolar caps" previously described. For this phase of the investigation we will utilize one and possibly two of each of the following types of carcinogenic chemicals. 1) Polycyclic hydrocarbons. 2) Aromatic amines. 3) Amino-azo dyes, and 4) Alkylating agents. The second phase of the experiment, which will continue next year will be an attempt to determine whether any of the previously described biochemical effects of 4-Nitroquinoline N-Oxide are responsible for the "Nucleolar caps". This will involve treating the cells with carcinogenic and noncarcinogenic agents having proven ability to 1) React with S-H groups, 2) Decrease intracellular ATP, 3) Inhibit uptake of P^{32} and C^{14} into nucleic acids and protein respectively. This latter study will not be described in detail at the present time.

DETAILED PLAN OF PROCEDURE:

For purpose of simplification the type of experiment to be performed will be described with one chemical, the alkylating agent mechlorethamine - HCL (nitrogen mustard). Similar experiments will be carried with the other carcinogenic agents. A 10^{-5} Molar concentration of mechlorethamine in Hank's balanced salt solution will be placed on Chang liver cells for a period of ten minutes and then replaced by normal culture media (This is the procedure giving the best results with 4-Nitroquinoline N-Oxide). The cells will be growing in Rose chambers or on cover slips in ointment jars. The sequential changes in the cell, with special reference to the nucleoli, will then be photographed continuously by phase time-lapse motion picture microscopy. At stated intervals cover slip preparations will be fixed for routine histologic stains (i.e., H & E), histochemistry (i.e., acridine orange, azure B., and a battery of enzyme histo-chemical reactions including ATPase, acid and alkaline phosphatases, glucose 6-dehydrogenase) and electron microscopy. Similar experiments will be conducted with the following agents: 1) Polycyclic hydrocarbons - DMBA(9, 10 dimethyl 1, 2 benzanthracene) and methyl cholanthrene; 2) Aromatic amine - 2 napthylamine; and 3) Amino-azo dye - 4-dimethylamino-azobenzene.

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DISCUSSION:

The demonstration of a consistent morphologic change in the cell nucleolus produced by a carcinogenic chemical is of great theoretical importance, since it gives a clue concerning the site of action of at least one chemical carcinogen. Hitherto no morphologic clue of a compound's potential carcinogenic activity has been available to investigators. Should the "nucleolar caps" be characteristic of one or more groups of chemical carcinogens we would then have a tool which could provide a single, rapid, test of carcinogenic activity. Correlation of such a morphologic change with specific biochemical activity is of obvious importance. These studies with 4-Nitroquinoline N-Oxide and other carcinogens may provide such a correlation between morphologic and biochemical data.

BIBLIOGRAPHY

1. Abstract: 219 "Nucleolar Caps" Produced By the Carcinogenic Agent 4-Nitroquinoline N-Oxide. R. C. Reynolds, M.D. and P.O'B. Montgomery, M.D. Proceedings of the American Association for Cancer Research Vol. 3, No. 4, pg. 354, March 1962.

2. Nakahara, Waro, Critique of Carcinogenic Mechanism. Prog. Exp. Tumor Res. Vol. 2, pp. 158-202.

6. Budget Plan:

a.	Salaries	$4,384.00
b.	Expendable Supplies	8,000.00
c.	Permanent Equipment	2,000.00
d.	Overhead (15% of a,b,e)	2,008.00
e.	Other	1,000.00
	TOTAL	$17,392.00

- - - - - - - - - - -

Salaries

Laboratory Assistant - ($4200 per annum)	$4,200.00
OASI & WCI	184.00

Expendable Supplies

Tissue Culture Supplies, Glassware Electron Microscope Supplies, Film Glass & Diamond Knives, Chemicals	8,000.00

Permanent Equipment

Optical Equipment, Electronic Timers, Time Lapse Phase Microscope Equipment, Tissue Culture Chambers	2,000.00

Other

Travel for visitation to other laboratories, attendance at scientific meetings Travel to cover actual travel expenses	1,000.00

Direct Costs	$15,384.00
Overhead (15% of direct costs (exclusive of permanent equipment)	2,008.00
	$17,392.00

Investigator reserves the right to transfer funds from one category to another as the need arises.

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7. Anticipated Duration of Work: THREE YEARS

(Present Request - 9/1/62 to 8/31/63)

8. Facilities and Staff Available:

Staff: Full-time electron microscopy, tissue culture, and histochemistry technicians. Senior electronics engineer full-time; 4-assistant electronic engineers. One pathology resident and 8 part-time medical students.

Facilities: Three phase contrast time lapse motion picture units. A Baker interference microscope. RCA electron microscope and dark room facilities. Two Porter-Blum ultra microtomes. Reichert fluorescent microscope. The flying spot ultraviolet and interference microscopes will be available if their use is indicated.

9. Additional Requirements: NONE

10. Additional Information (Including relation of work to other projects and other sources of supply):

The presently constituted laboratory is jointly supported by the Damon Runyon Memorial Fund for Cancer Research, the Atomic Energy Commission-Division of Biology and Medicine, the Southwestern Medical Foundation, and the National Aeronautics and Space Administration.

The principle efforts of the section laboratory under supervision of Dr. Reynolds are directed towards the elucidation of the role of the nucleolus in experimental carcinogenesis and viral replication.

Signature R. C. REYNOLDS, M. D.
Director of Project
P. O'B. MONTGOMERY, M.D.

E. A. GELL
Business Officer of the Institution

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CARDIOVASCULAR, PHARMACOLOGY, CHEMISTRY

#321 R1
Activated - 8/1/61

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

Committee:
Dr. Jacobson, Chm.
Dr. Bing
Dr. Cattell

APPLICATION FOR RESEARCH GRANT (RENEWAL)

Date: May 1, 1962

1. Name of Investigators: ROBERT A. KUHN, M. D.
HERMANN KUGLER, M. D.

2. Title: Associate Professor

3. Institution & Address: R. A. KUHN, M. D., - Department of Neurosurgery,
New York Medical College
Fifth Avenue at 105th Street
New York, New York
Division of Neurosurgery, All Souls Hospital,
Mt. Kemble Avenue, Morristown, New Jersey

HERMANN KUGLER, M. D., - Resident in Neurology
Metropolitan Hospital
New York, New York.

4. Project or Subject: "EFFECT OF TOBACCO UPON CEREBRAL CIRCULATION"

5. Detailed Plan of Procedure:

During the past year, under the auspices of the Tobacco Industry Research Committee, a definitive work has been accomplished in setting normal standards for velocity of blood flow through the human brain. Knowledge of these basic values was essential before any attempt could be made to study variants, whether developmental or environmental.

A new research tool perfected by the chief investigator, was used to study blood flow-cerebral angiography performed in such manner as to result in physiological flow of contrast media. When this technique is combined with high speed film-shuttling, a permanent record is obtained of all phases of neck and brain circulation. A color, sound movie demonstrating the method, and its remarkable potential for investigation of cerebral blood flow, is to be presented together with a static exhibit of the technique at the A.M.A. annual meeting in June, 1962. This movie incorporates a brief, and relatively crude initial effort to display the circulation in cine fashion.

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Measurement of the phases of cervical-cerebral flow has been accomplished during the past year by study of consecutive individual, 14 x 14" cut-films, exposed at a speed of six films per second for five seconds. During this investigation it became apparent that moving picture sequences and slow motion display of the cerebral capillary phase - or any other selected phase - was feasible. The angiographic method made it possible to position the patient so that each film could be precisely superimposed upon the next - and a new method of photographing X-rays has yielded positive prints of exceptional quality.

It is planned to combine these techniques in the coming year to construct film strips, in slow motion of the important capillary phase of brain circulation. These strips can then be analyzed for differences in consecutive studies of the same patient, and between different patients. The effects of tobacco smoke inhalation, if any, can be objectively evaluated. The film strips will be combined into a movie which, it is believed, will receive wide dissemination as the first teaching film on phases of cerebral circulation. If these ends are accomplished, and there seems every reason to believe they are attainable, results should constitute an important milestone in modern knowledge of cerebral hemodynamics.

6. Budget Plan:

a.	Salaries *	$18,000.00
b.	Expendable Supplies *	4,000.00
c.	Permanent Equipment *	2,200.00
d.	Overhead (15% of a,b,e)	3,420.00
e.	Other	800.00
	TOTAL	$28,420.00

a. *SALARIES - R. A. Kuhn, M. D. - Considerable success has attended initial efforts to define phases of cerebral circulation, and in particular to determine for the first time normal values of blood flow velocities in the human brain. Following research lines in the direction outlined in the original application to the T.I.R.C., it is the hope of the principal investigator to expand these data by devoting additional time withdrawn from the private practises of neurology and neurosurgery. The amount requested will enable the exercise of considerable freedom in attaining research objectives.

H. Kugler, M. D. - Continuation and expansion of services as previously rendered. Dr. Kugler will, in addition, be responsible for workup of clinic patients, and assembling pertinent data for each of their records. Dr. Kugler performs a particularly valuable service because of his multilingual abilities, and excellence as a library research worker. He has access to all facilities of the New York Academy of Medicine.

b. *EXPENDABLE SUPPLIES - During recent preparation of a teaching film, shortly to be generally released, and entitled "A New Diagnostic Technique for Strokes: Retrograde Brachial Angiography", it became apparent that moving picture sequences of opaque media passing through the brain could be accurately constructed and displayed by making composites of individual prints of the six-per-second cut-film X-rays. This process has not previously been utilized,

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b- cont'd - and offers excellent opportunity for slow motion study of the capillary phase of cerebral circulation. In addition, it will be used extensively for analysis of other phases of cerebral circulation. The process of creating these movies is somewhat laborious, for a positive print must be made of each of thirty films, and then each print photographed and reprinted. It is planned to combine film strips from different patients into a movie demonstrating discrete phases of cerebral circulation.

c. *PERMANENT EQUIPMENT - An automatic injector (Cordis) will enable rapid, controlled injection of variable amounts of contrast medium, accurately timed to the x-ray apparatus. It will therefore perform the vital function of removing the angiographer from otherwise cumulative exposures to radiation. It will also help provide a standard set of angiograms, since identical times can be programmed for the injection in each patient.

7. Anticipated Duration of Work: ONE YEAR. It is planned to present results of this research at the American Neurological Association meeting in 1963.

8. Facilities and Staff Available:

Studies will be concentrated in the All Souls Hospital, Division of Neurosurgery. This division is under the direction of Dr. Kuhn. The previous full cooperation of the Administration of All Souls Hospital assures continued access to clinic as well as private patients - and will provide access in an investigative atmosphere difficult to create in an institution hampered by a multitude of municipal rules and regulations.

Comparison films of patients at Metropolitan Hospital, New York City, will be available to serve as controls. Although these studies will be performed on slower angiographic equipment, speeds are sufficiently great to allow valid comparisons.

9. Additional Requirements: A supplementary amount may be requested during the year for cost of reprints of papers published as work progresses.

10. Additional Information (including relation of work to other projects and other sources of supply)

Other sources of supply - NONE

Certain of the subjects included in this study will constitute part of an evaluation program of stroke patients being conducted privately by the principal investigator. Also, some films used in the control series will be those of patients in a cerebrovascular disease program, and under investigation by the neurology and neurosurgical services of New York Medical College.

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Signature ROBERT A. KUHN, M. D.
Director of Project

SISTER MARY ELEANOR - Administrator
Business Officer of the Institution

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CARDIOVASCULAR, PHARMACOLOGY and CHEMISTRY #339

Committee:
Dr. Bing, Chm.
Dr. Cattell
Dr. Jacobson

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, N.Y.

Application for Research Grant

Date: January 31, 1962

1. Name of Investigator: E. T. ANGELAKOS, M. D., PH.D.

2. Title: Associate Professor of Physiology

3. Institution & Address: Boston University School of Medicine
Department of Physiology
80 East Concord Street
Boston, Massachusetts

4. Project or Subject: "RELEASE OF CATECHOL AMINES FROM THE ISOLATED HEART"

5. Detailed Plan of Procedure:

There is now ample evidence that within the connective tissue of the heart there is a significant number of chromaffin cells which in all probability contain appreciable quantities of catechol amines especially epinephrine (1, 3, 4, 6). The role of the possible liberation of catechol amines in cardiac physiology is at present obscure. However, there is evidence that catechol amines are liberated following an adequate stimulus. Notably larger amounts of acetylcholine (Ach) have been shown to produce catechol amine liberation in the heart (1,2).

The purpose of the proposed investigation is to study the ability of certain compounds to release catechol amines from the isolated heart in vitro. It is anticipated that such a study will provide some insight and in particular it will serve to elucidate the pharmacological characteristics of catechol amine liberation. Information about catechol liberators will be of particular value since such substances may serve as "pharmacological tools" in future studies.

There is some suggestive evidence that the cardiac chromaffin tissue may be physiologically and pharmacologically similar to the adrenal medulla and hence to be akin to autonomic ganglia. In this connection there is a direct relation to nicotine which exhibits both ganglionic stimulant and depressant properties and will be used in this study for this purpose. In fact the pharmacological characteristics of catechol amine liberation by Ach are such, that this action of Ach has been classified as "nicotinic" (1).

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The methods to be used are relatively simple and some of them have been in constant use in this laboratory for some time. The isolated preparations will include rabbit, guinea pig and cat atria and rabbit and rat hearts perfused with ionically balanced buffered solutions. Determination of catechol amines will be made in the effluent. Catechol amine isolation, determination and separation will be made using the recently developed techniques. This will include adsorption on alumina, eluation, oxidation and determination of the fluorescent product with an ultraviolet fluorometer (5,6). Paper chromatograms will also be studied.

Mechanical and electrical responses of all the preparations will be continuously recorded through special amplifiers, transducers and recorders now available and in operation in this laboratory. Thus it will be possible to determine in addition the immediate mechanical and electrical manifestations of catechol amine liberation.

In controlled experiments reserpine and similar compounds will be used to deplete the catechol amine stores and comparison will be made between normal and depleted hearts. Furthermore, inhibitors of the known catechol metabolizing enzymes (O-methyl-tranferase and mono-amine oxydase) will be used in vivo and in vitro to increase the catechol amine content and recovery of released amines (7). A perfusate rich in ascorbic acid will be used in all cases to reduce the rate of autoxidation of released catechols.

Preliminary plans have been made so that the early part of this study may be conducted in Dr. von Euler's laboratory (Karolinska Institute, Sweden) where the principal investigator plans to spend a period of time in order to become more familiar with current techniques of catechol amine identification and measurement, and to study various other aspects of catechol amine release. Dr. von Euler's group is now actively engaged in the problem of catechol amine liberation and a collaboration with that group during the early phases of the proposed project would be most fruitful. Part of the funds to cover the principal investigators trip to Sweden will be provided for by a Career Development Award Grant from the U.S. Public Health Service to the principal investigator.

REFERENCES

1. Hoffman F., Hoffman, E. J., Middleton, S. and Talesnik, J., The Stimulating Effect of Acetylcholine on the Mammalian Heart and the Liberation of an Epinephrine Like Substance by the Isolated Heart, Am. J. Physiol., 144:189, 1945.

2. Ginzel and Kottegoda, S.R., Nicotine-like Action in Auricles and Blood Vessels after Denervation, Brit. J. Pharmacol., 8:348, 1953.

3. Raab, W. and Gigee, W., Norepinephine and Epinephine Content of Normal and Diseased Human Hearts, Circulation, 11:593, 1955.

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4. Day, M. The Release of Substances Like Acetylcholine and Adrenaline by the Isolated Rabbit Heart, J. Physiol., 134:558, 1956.

5. Underfriend S., Survey of Chemical and Physical Methods for Measuring Physiological Amounts of Catechol Amines in Symposium on Catechol amines, Pharm. & Exp. Therap. Study Section NIH, 1958.

6. von Euler, U.S. Autonomic Neuroeffector Transmission in Handbook of Physiology, I:215, 1959.

7. Crout, J. R., Creveling, C. R. and Underfriend S., Norepinephrine Metabolism in the Rat Brain and Heart, J. Pharm. Exp. Therap. 132:269, 1961.

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ITEMIZED BUDGET

	1962-63	1963-64
Salaries		
Technical Assistance (1)	$4,500.00	$4,500.00
Fringe Benefits (7.5%) (2)	238.00	238.00
Permanent Equipment		
Turner Fluorometer (3) (with accessories)	2,000.00	
Supplies		
Chemical & Laboratory Suppl. (1)	800.00	800.00
Animals	300.00	300.00
Travel (4)	600.00	200.00
Reprints & Publ. Costs	250.00	250.00
	$8,688.00	$6,288.00

TOTAL FOR TWO YEARS: $14,976

(1) Authorization is requested that part of the above funds for technical assistance and/or laboratory supplies may be used at the Karolinska Institute in Sweden (Dr. von Euler's Laboratory). Boston University would be authorized to make advances and/or reimbursements for such expenditures.

(2) According to general Boston University Policy.

(3) This instrument is essential for the fluorimetric determinations of catechol amines.

(4) It is also requested that the budgeted travel funds may be used to defray travel expenses connected with the visit and stay in Sweden of the principal

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investigator. However, part of this cost will be provided by another source. (Career Development Fellowship Grant by USPHS).

It is understood that all funds expended in USA or Sweden will be in connection with the above outlined project and specific accounts of all expenditures will be given.

6. Budget Plan: (Based on a two year program)

a.	Salaries	$9,476.00
b.	Expendable Supplies	2,200.00
c.	Permanent Equipment	2,000.00
d.	Overhead (15% of a,b,e)	1,946.00
e.	Other	1,300.00
	TOTAL	$16,922.00

7. Anticipated Duration of Work: June 1, 1962 to May 31, 1964

8. Facilities and Staff Available: All the laboratory facilities necessary for the performance of the proposed studies are available. This includes laboratory space, animal quarters and a large number of electronic equipment necessary for measuring electrophysiological and contractile responses in isolated hearts.

9. Additional Requirements: Funds are requested for full time technical assistance to be used in connection with this project and for supplies. The only major item needed is a Turner Fluorometer for the determination of catechol amines.

10. Additional Information (including relation of work to other projects and other sources of supply)

This project is an outgrowth of studies now in progress on the excitatory effects of acetylcholine in the heart (Supported by the American Heart Association). No source of support is available at present for the study of the specific problem of catechol amines release. The results of this project will be correlated with other studies on the electrophysiology of the heart performed in this laboratory under the direction of the principal investigator.

Signature E. T. ANGELAKOS, M. D. PH.D.
Director of Project

Kurt M. Hertzfeld
Business Officer of the Institution

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Pathologic-Diagnostic

Committee:
Dr. Kotin, Chairman
Dr. Lynch
Dr. Reimann

#342

TOBACCO INDUSTRY RESEARCH COMMITTEE

150 East Forty Second Street New York 17, N.Y.

Application for Research Grant

Date: February 21, 1962

1. Name of Investigator: Daniel Stowens, M.D.

2. Title: Director of Laboratories, Associate Professor of Pathology.

3. Institution & Address: Children's Hospital, 226 E. Chestnut St., Louisville, Ky. University of Louisville School of Medicine, 101 W. Chestnut St., Louisville, Ky.

4. Project or Subject: Effect of automobile exhausts on the tracheal-bronchial tree and lung: an experimental study.

5. Detailed Plan of Procedure:

Several studies have correlated the degrees of air pollution with the exacerbation of chronic or pre-existing pulmonary disease. There have also been some reports relating a possible connection between air pollution (especially that portion contributed by motor vehicles) with increased incidence of carcinoma of the lung. The purpose of the proposed study is to determine experimentally whether automobile exhaust products produce anatomic lesions in experimental animals and, if so, to determine what fraction of the exhaust is responsible.

Automobile exhaust products will be collected by the attachment of a compressor to the exhaust system of a standard automobile. The entire exhaust mass will be brought to 150 pounds per square inch pressure. At this pressure, it has been determined by previous work and analysis that 99% of the compounds which have a boiling point above -10°C., will be precipitated. The component of the exhaust remaining in a gaseous state at this pressure consists mainly of nitrogen, carbon dioxide and carbon monoxide. The gaseous portion will be vented to the exterior.

(The principal investigator has previously built and operated successfully such a device.) The necessity for collection of exhaust material in this fashion is dictated by the fact that, using such a condensate, it will be possible to insure adequate oxygen levels in the re-suspended atmosphere and to avoid toxic accumulations of carbon monoxide.

Experimental animals will be housed in cages which will be placed in closed rooms in which the atmosphere and concentration of air pollutants will be able to be controlled. Re-suspension of the condensed exhaust material will be by means of a standard nebulizer (manufactured by Thomas Industries) operated by a small compressor. This nebulizer is capable of producing particles of the size of 4 micra.

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The experiments will involve varying the concentration of pollutants in the atmosphere; varying the length of time of exposure of the animals to the air pollutants, and by testing the effects of the two major fractions of the exhaust on the animals, the water extractable portion and the chloroform extractable portion. Animals will be sacrificed and histopathological studies of the tracheo-bronchial tree and lung will be performed.

6. Budget Plan:

a.	Salaries	9,000.00
b.	Expendable Supplies (incl. animals & upkeep)	2,000.00
c.	Permanent Equipment	500.00
d.	Overhead (15% of a, b, e)	1,725.00
e.	Other	500.00
	Total	$13,725.00

7. Anticipated Duration of Work: One to two years.

8. Facilities and Staff Available:

Histopathology laboratory, photomicrographic laboratory, animal house, research assistant, diener.

The Children's Hospital is an integral part of the University of Louisville School of Medicine and considerable professional, technical and other support is available from the School.

9. Additional Requirements:

No additional requirements are anticipated. However, it may be necessary to perform certain gas analyses for which outside assistance on a contract basis might be necessary.

10. Additional Information (Including relation of work to other projects and other sources of supply):

This project is an attempt on the part of the principal investigator to correlate his interests in what, until the present, have been two separate fields of study; the possible causes of tumors in general, and air pollution. At the present time no support for the research from other sources has been obtained.

Signature Daniel Stowens
Director of Project

Fredric R. Heeder
Business Officer

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BIOASSAY, CARCINOGENESIS and TISSUE CULTURE March 1, 1962

COMMITTEE:
Dr. Jacobson, Chm.
Dr. Kotin
Dr. Wilson

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

#343
(Compare #295
denied 2/10/61)

APPLICATION FOR RESEARCH GRANT

Date: February 13, 1962

1. Name of Investigator: MARTIN S. PROTZEL, B.S., D.D.S.

2. Title: Chief, Department of Oral Pathology

3. Institution & Address: Martland Medical Center
65 Bergen Street
Newark, New Jersey

4. Project or Subject: "A COMPARATIVE STUDY OF THE EFFECTS OF 3-METHYLCHOLANTHRENE AND CIGARETTE SMOKE CONDENSATE APPLIED TO THE ORAL TISSUES OF SWISS MICE (ICR) CONDITIONED WITH ALCOHOL AND/OR CARBON TETRACHLORIDE".

5. Detailed Plan of Procedure: Randombred Swiss Mice (ICR) will be employed as the experimental animal. One group of animals (A) will be painted with a 0.3% solution of 3-methylcholanthrene in acetone on the mucosal surfaces of the lip and cheek. A second group of animals (B) will be painted with a 50% solution of cigarette smoke condensate in acetone at the same sites as animals in group "A". Animals in the control group (C) will be painted with an isotonic saline solution at the same sites as animals in groups "A" and "B". All groups of animals will be painted four times weekly; a cotton applicator will serve as the instrument for swabbing the oral tissues. Animal groups "A", "B" and "C" will be subdivided into four sub-groups. Animals in Groups "A"-1, "B"-1, "C"-1 will have a 15% ethyl alcohol solution in water for drinking, ad libitum and will be given a subcutaneous injection once every week of 0.06 cc of a 50% solution of carbon tetrachloride in mineral oil. Animals in groups "A"-2, "B"-2, "C"-2 will have the alcohol for drinking however, the carbon tetrachloride will not be injected. Animals in groups "A"-3, "B"-3, "C"-3 will have water for drinking, ad libitum, however, they will be injected with carbon tetrachloride. Animals in groups "A"-4, "B"-4, "C"-4, will have water for drinking, ad libitum, carbon tetrachloride will not be injected. Ninety-six animals will comprise each group with twenty-four in each sub-group for a total number of two hundred and eighty-eight. Each sub-group will have twelve males and twelve females. Animals will be housed in stainless steel cages, six to a cage. A standard laboratory chow for mice will be provided. Cages will be cleaned and sterilized once a week. Animals will be observed daily. Initial and progressive changes noted clinically will be recorded and photographed. When a malignant process is observed, the animal will be sacrificed by the exsanguination method. Blood will be obtained from the right ventricle of the heart and will be collected in sterile tubes, then sent to the Biochemistry Department for electrophoretic

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studies of serum proteins (total protein, Albumin, alpha 1, alpha 2, Beta and Gamma globulins). Individual electrophoretic patterns will be traced on graph paper and evaluated. Complete autopsies will be performed on each animal, special attention will be given to the analysis of the oral tissues, liver and cervical lymph nodes. All organs, however, will be carefully studied grossly and microscopically. The livers of all animals will be stained with Sudan IV as well as routine H.and E. for microscopic analysis.

6. Budget Plan:

a.	Salaries	$14,000.00
b.	Expendable Supplies	1,827.00
c.	Permanent Equipment	3,005.00
d.	Overhead (15% of a, b, e)	2,449.05
e.	Other	500.00
	TOTAL	$21,781.05

7. Anticipated Duration of Work: ONE YEAR

8. Facilities and Staff Available:

There are four animal rooms available adjacent to one another on a special floor in the hospital. Each room is approximately 25' x 15' with finished walls and vinyl floors. Modern sinks and cabinets are present in each room. One room contains a refrigerator and two steam sterilizers. Mobile Mayo surgical stands and castle operating room lights are available as well as a surgical cabinet with suitable instruments. Two rooms are being equipped with air conditioners. The pathology, hematology and biochemistry laboratories are well equipped and staffed to render the service and material for this project. The animal cages (30) and cage stands (2) however, are constructed of galvanized iron and are inadequate both in number and composition for this project.

The members of the staff available for this project include Dr. Edwin H. Albano, Dr. Thomas A. Santoro, of the Department of Pathology of the Martland Medical Center. Laboratory assistants in all of the departments of Pathology are also available.

9. Additional Requirements:

Stainless steel cages for mice, with racks
Assistant for the animal caretaker
Food Containers
Air conditioners (2) one-ton units

10. Additional information (including relation of work to other projects and other sources of supply)

During the past 20 years, I have examined scores of patients with oral cancer. Consistently, these patients yielded histories of drinking alcoholic beverages over a long period of time, and admitted to the excessive use of tobacco. Clinically, these patients also exhibited concomittant evidence of dietary deficiencies. It is my opinion that individuals who are constant drinkers of alcoholic beverages and have concommittant dietary deficiencies develop liver damage. Liver damage with functional imbalance over a period of time renders

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the oral mucosal tissues more susceptible to the action of chemical carcinogens. It is possible, therefore, that liver imbalance which precedes the development of oral cancer is an important cocarcinogenic factor. Thus, over a long period of time, a weak carcinogen acting constantly on a susceptible oral mucosa could induce cancer. Statistical studies of Trieger, Taylor and Weisberger and R. C. Vincent of Roswell Park Memorial Institute confirm these observations. In a recent article in the Journal of the American Medical Association, Herbut, Tsaltus and Kraemer suggest the possibility of a tumor inhibitory principle present in the liver which when deficient, either general or local, could be responsible for the development of cancer. To determine whether liver damage is an important cocarcinogenic factor in the development of oral cancer, a preliminary animal experiment was performed at the Martland Medical Center Laboratory. This study was completed recently and is being prepared for publication. For this study, thirty randombred Swiss Albino mice were employed. Liver damage in the form of fatty infiltration was induced by the weekly injection of a 0.06 cc solution of carbon tetrachloride in mineral oil and/or the use of a 15% solution of ethyl alcohol for drinking. The chemical carcinogen was a 3-methylcholanthrene which was employed as a 0.3% solution in acetone and applied to the oral mucosal surfaces of the lip and cheek of the animals four times weekly. Animals painted with the carcinogen and receiving carbon tetrachloride and alcohol developed tumors eight weeks sooner than the animals which were merely painted with the carcinogen. Malignant changes from initial papilloma to frank carcinoma developed more rapidly in the former group of animals than in the latter. Histologically, the malignant tumors were squamous cell carcinoma varying from Grade I to Grade III. Employing routine H. and E. and special Fat Stain, Sudan IV, the livers of these animals exhibited fatty infiltration. Electropheretic studies of the proteins of these animals disclosed abnormalities of albumin, albumin-globulin ratio and alpha, beta and gamma globulin. These results indicated liver imbalance. Although not conclusive, the sum total of these results indicated that when liver imbalance exists in the experimental animal, the oral mucosal tissues are more susceptible to the action of a chemical carcinogen. We realize that the use of thirty animals for this study represents too small a number for critical or conclusive evaluation. It is possible, however, that results obtained employing a large number of animals (288) subjected to the same experimental procedures performed in the preliminary study would prove to be more conclusive.

Signature MARTIN S. PROTZEL, B.S., D.D.S.
Director of Project

G. O. ROTUNDA
Business Officer of the Institution

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REFERENCE TO PUBLISHED ARTICLES APPLICABLE TO THIS EXPERIMENT

1. Wynder, E.L., Bross, I.J. and Feldman, R.M.: A Study of the Etiological Factors in Cancer of the Mouth. Cancer 10:1300-1323, 1957.

2. Wynder, E.L., Bross, I.J., and Day, E.: A Study of Environmental Factors in Cancer of the Larynx. Cancer 9:86-110, January, February, 1956.

3. Wynder, E.L., Hoffman, D.: The Carcinogenicity of Benzofluoranthenes. Cancer (Philad) 12/6 1959, 1194-1199.

4. Wynder, E.L., Wright, G.F. and Lam, J.: A Study of Tobacco Carcinogenesis. VI. The Role of Precursors. Cancer (Philad) 12/6 1073-1078, 1959.

5. Wynder, E.L., and Hoffman, D.: A Study of Tobacco Carcinogenesis VII. The Role of Higher Polycyclic Hydrocarbons. Cancer (Philad) 1959. 12/6 1079 - 1086.

6. Kreshover, S.J. and Salley, J.J.: Predisposing Factors in Oral Cancer. J. Am. Dental Assoc., 54:509-514, 1957.

7. Levy, B.M.: The Experimental Production of Carcinoma of the Tongue in Mice. J. Dental Res. 37:950, 1958.

8. Goldhaber, P.: The Role of Saliva and Other Local Environmental Factors in Oral Carcinogenesis. J. Am. Dent. Assoc. 54:517-423, 1957.

9. Toto, P.P. Tumors of the Gingiva. In Robinson, H.B.G. Ed. Tumors of the Oral Regions. Phil., W.B. Saunders Co., 1958.

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11. Croninger, A.B.; Graham, E.A.; and Wynder, E.L.: Experimental Production of Carcinoma with Different types of Tobacco Tars. Proc. Am. A. Cancer Res. 2:289, 1958.

12. Editorial: J. Oral Surg. 15:80, Jan. 1957.

13. Korbler, J. and Frank, P., and Turner, V.: Dependency of the Carcinogenic Effect of Tobacco Sediments on the Area of Application. Oncologia 12:22-27 No. 1. 1959.

14. Vincent, R.C.: Statistical Study, Tobacco, Alcohol and Liver Cirrhosis in Oral Cancer Patients, Medical Tribune, 1961.

15. Herbut, P.A.; Tsaltas, T.T. and Kraemer, W.H.: Natural Resistance of Animals to Cancer. J.A.M. A. 174: No. 7732-734, 1961.

16. Salley, J.J.: Epithelial Carcinogenesis in the Absence of Accessory Structures. Oral Surgery, Oral Medicine, Oral Pathology. 14: No. 12, 1478-84, 1961.

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17. Shear, M.J. and Leiter, J.: Studies in Carcinogenesis. Compounds Related to 20-Methylcholanthrene. J. Nat. Cancer Inst. 2:99-113, 1941.

18. Stowell, R.E. and Cramer, W.: The Effects of Solvents in Methylcholanthrene Epidermal Carcinogenesis. A Comparison of Benzene and Acetone. Cancer Research: 2,193-197, 1942.

19. Carruthers, C.: The Effect of Carcinogens on the Hepatic Vitamin "A" Stores of Mice and Rats. Cancer Research. 2: 168-173, 1942.

20. Adams, E.M., et. al.: Vapor Toxicity of Carbon Tetrachloride Determined by Experiments on Laboratory Animals. A.M.A. Archives of Industrial Hygiene and Occupational Medicine: 6, No. 1, 50-67.

21. Bergolits: Summary of Subcutaneous Injections of Carbon Tetrachloride in C57 Mice. Survey of Compounds Which Have Been Tested for Carcinogenic Activity-Supplement No. 1, U.S. Department of Health, Education and Welfare: 32, 1957.

22. Erf, L A. and Miller, B.J.: Is Cancer a Deficiency Disease? GP 15:75-79 April, 1957.

23. Wiest, W.G. and Heidelberger, C.: The Interaction of Carcinogenic Hydrocarbons with Tissue Constituents. Cancer Research. 13, No. 3; 246-262, 1953.

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CARDIOVASCULAR, PHARMACOLOGY and CHEMISTRY # 344

Committee:
Dr. Bing, Chmn.
Dr. Cattell
Dr. Wilson

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

COMPARE: #33
Activated - 2/1/55
Renewed - 2/1/56
#160
Activated - 8/1/57
#213
Activated - 5/1/59
Renewed - 5/1/60
#301
Activated - 5/1/61

APPLICATION FOR RESEARCH GRANT

DATE: March 9, 1962

1. Name of Investigator: WALTER REDISCH, M. D.

2. Title: EFFECTS OF TOBACCO ON THE HUMAN VASCULAR SYSTEM

3. Institution & Address: NEW YORK UNIVERSITY MEDICAL CENTER
550 First Avenue
New York 16, New York

4. Project or Subject: VASCULAR RESPONSES TO TOBACCO SMOKING IN PATIENTS WITH VASCULAR DISEASE.

5. Detailed Plan of Procedure:

(a) It is proposed that the investigation of vascular responses to tobacco smoking measuring blood flow to skin and muscle by segmental plethysmograph be continued in order to ascertain, whether the established correlation between responses in skin flow to smoking and skin sensitivity to intradermal tobacco extract in normal individuals holds true for patients with occlusive arterial disease.

(b) It is proposed that the effect of tobacco smoking on blood flow to the orbit of the eye of man be evaluated. The "pulsensor", developed by Dr. Thorner at the University of Pennsylvania's Department of Neurophysiology, has been purchased after a personal visit to Dr. Thorner's laboratory. It has been shown that blood flow to the orbita oculi is well representative of the blood flow at the base of the brain. The machine permits direct writing of pulse-curves with automatic pressure changes and fairly accurate determination of systolic and diastolic pressures in the vasculature of the orbit, separately determined on the right and on the left. Thus the effects of tobacco smoking on a vascular bed representative of a part of the brain blood flow can be studied.

(c) It is proposed that the effects of tobacco smoking on minute blood vessels of the skin and mucous membranes be studied with a capillaromicrophotographic apparatus which permits 400 x enlargement. The machine has been

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purchased from other funds available. The current studies with segmental plethysmography will be correlated with the pulsensor measurements and the minute vessel photography.

6. Budget Plan:

	1st Year	2nd Year	3rd Year
a. Salaries (1 technician	$4,400.00	$4,774.00	$5,148.00
Employee Fringe Benefits	286.00	334.00	386.00
b. Expendable Supplies	800.00	800.00	800.00
c. Permanent Equipment	none	none	none
d. Overhead	868.00	931.00	995.00
e. Other (travel)	300.00	300.00	300.00
TOTAL	$6,654.00	$7,139.00	$7,629.00

7. Anticipated Duration of Work: THREE YEARS

8. New York University Research Service, Goldwater Memorial Hospital, facilities with all apparatus (man plethysmograph, dog-plethysmograph and pulsenor).

Also New York University Medical, Neurological and Neurosurgical Wards at Bellevue.

STAFF AVAILABLE: Dr. Walter Redisch, Dr. Harbans Singh, Dr. Heinz Wittig, Mr. Edward Messina and Mr. Emmet Clemente.

9. Additional Requirements: Mixed tobacco cigarettes, as currently supplied.

10. Additional information (including relation of work to other projects and other source of supply)

This work will be in part based on the previous work done together with Dr. Marion B. Sulzberger and Dr. Vincent J. Fontana. The investigator is also associate investigator on the extracranial vascular occlusion project (NIH No. HP 7018) at Bellevue Hospital and will be able to correlate the tobacco studies on the pulsenor with the above study.

Approved:

GEORGE E. ARMSTRONG

George E. Armstrorg, M.D., Director

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CARDIOVASCULAR, PHARMACOLOGY and CHEMISTRY

No. 345
cf. No. 155

COMMITTEE:
Dr. Cattell, Chm.
Dr. Jacobson
Dr. Wilson

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, N. Y.

Activated: 7/1/57
Extended to 9/1/58
Renewed: 9/1/58

APPLICATION FOR RESEARCH GRANT

Date: APRIL 4, 1962

1. Name of Investigator: DUANE G. WENZEL, PH.D.

2. Title: Professor of Pharmacology

3. Institution and Address: School of Pharmacy
University of Kansas
Lawrence, Kansas

4. Project or Subject: "A STUDY OF CENTRAL ACTIONS OF NICOTINE"

5. Detailed Plan of Procedure:

INTRODUCTION:

The use of tobacco induces a pleasurable feeling that can not be adequately described as "tranquilization" or "stimulation". There are indications that such an effect is related to the release of catecholamines, presumably within the brain itself. This evidence is not entirely adequate, for it has been related to nicotine-induced convulsions rather than to moderate signs of a central action. Such convulsions, however, are blocked not only by various adrenergic blocking agents, but by atropine-like compounds. This activity of the latter group indicates acetylcholine as the mediator affecting catecholamine release.

In view of the therapeutic value of amine oxidase inhibitors and the so-called psychic energizers in various depressive states, it is proposed that the central mechanism of nicotine, other than the convulsive effects, be more closely examined, particularly in reference to its potential interaction with various psycho-therapeutic agents.

Although nicotine has been frequently tested for various central actions, such tests have usually been based upon inadequate methodology and poor experimental design. In the tests to be outlined, adequate numbers of animals are to be employed with graded doses of nicotine, and the results are to be subjected to modern statistical analysis.

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In all tests where changes from control values are obtained, it is planned to repeat the study with the simultaneous administration of otherwise ineffective doses of an adrenolytic and a parasympatholytic agent. A monomine oxidase inhibitor will be similarly employed to observe possible potentiation of catecholamine-related effects.

A. SPONTANEOUS ACTIVITY

Nicotine is to be administered in the drinking water of separate groups of mice in doses corresponding to approximately 1/8, 1/2, and 2 packs of cigarettes per day for 20 weeks. Activity of all experimental groups and a control will be determined initially and at weekly intervals for the 20 week period. Activity measurements will be made with photoelectric cages. Groups demonstrating statistically different activity will be tested as previously indicated with an adrenalytic, parasympatholytic, and an amine oxidase inhibitor.

B. FALL TIME FROM A ROTATING ROD

Mice are to be chronically treated with nicotine as above. They are then to be administered reserpine and chlorpromazine in doses inducing a minimal change in fall time and observed for changes from the "reserpine control" and "chlorpromazine control" fall times.

C. PHYSICAL EFFICIENCY OR ENDURANCE

The effects of smoking upon physical efficiency has been widely studied in humans with equivocal results. It is proposed that mice chronically treated with nicotine be tested for their swimming endurance at weekly intervals over the 20 week test period. Again the mechanism of any change from control values would be sought.

D. PARKINSONIAN TREMOR

A parkinson-like reaction from large doses of reserpine has been thought to be related to the release of brain dopamine. As nicotine has been employed to induce tremors in experimental animals, the potential interaction of reserpine and nicotine in this effect will be tested with rabbits and rats.

E. STARTLE REACTION

Rats chronically treated with nicotine are to be compared with controls for the magnitude of the "startle reaction". An auditory stimulus is to be provided by a pistol shot and the magnitude of the response related to displacement of a spring-mounted cage.

F. EMOTIONAL REACTIVITY

Rats of the previous test (E) would also be observed to determine alterations in emotional reactivity. Using a rating scale of 0 to 4, as proposed by others, the following would be evaluated: resistance to capture in home cage, resistance to handling, muscular tension, squealing and vocalization, urination and defecation, aggressive reaction to forceps close to snout, and aggressive reaction to prodding.

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G. LSD-INDUCED BEHAVIORAL CHANGES

LSD in experimental animals induces characteristic alterations in behavior. Such alterations may be blocked or modified with suitable psychotherapeutic agents. Modification of such LSD effects by nicotine would be initially studied in the Siamese fighting fish and guppies, and in chronically-treated mice. Further studies may be called for in the presence of nicotine-induced modifications.

It is proposed that the above studies constitute an initial exploration of the central actions of nicotine. Contingent upon the results obtained, further work may be called for using more complex animal behavioral responses.

6. Budget Plan:

a.	Salaries	$6,200.00
b.	Expendable Supplies	800.00
c.	Permanent Equipment	400.00
d.	Overhead (15% of a,b,e)	1,095.00
e.	Other	300.00
	TOTAL	8,795.00

7. Anticipated Duration of Work: ONE YEAR, June 1, 1962 through May 31, 1963.

8. Facilities and Staff Available:

FACILITIES: Several modern air-conditioned pharmacology laboratories and animal quarters are available for the conduct of this study. The usual items of pharmacological equipment and a number of specialized pieces of apparatus are available should the problem expand beyond the original concepts.

STAFF: The project director will personally initiate and conduct this study during the summer of 1962. A pharmacologically trained research associate and two laboratory technicians are to directly work on the project and continue it throughout the year under the project directors supervision.

9. Additional Requirements: NONE

10. Additional information(including relation of work to other projects and other sources of supply):

The methods employed in the proposed study have been used by the director of the project and he is familiar with the pharmacological effects of nicotine upon experimental animals in the doses to be used.

The following references are related to testing methods or nicotine studies by the project director.

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1. Antispasmodic and Related Pharmacological Actions of Some gamma-Arylpropylamines, J. Am. Pharm. Assoc., 45, 414 (1956).

2. Central Stimulating Properties of Some Terpenones, Ibid., 46, 77 (1957).

3. The Effect of Nicotine on Experimental Hypercholesterolemia in the Rabbit, Ibid., 47, 338 (1958).

4. The Effect of Nicotine on Hyperchloesterolized Cockerels, Ibid., 48, 115 (1959).

5. The Relative Reliability of the Escape Reaction and Righting-Reflex Sleeping times in the Mouse, Ibid., 48, 90 (1959).

6. Effect of Nicotine on Cholesterol-Induced Atherosclerosis in the Rabbit, Circ. Res., 1, 256 (1959).

7. Cardiovascular Interaction of Nicotine, Ergonovine and Hypercholesterolemia in the Rabbit, Circ. Res., 9, 694, (1961).

8. Effects of Centrally-Acting Drugs on Human Motor and Psychomotor Performance, J. Pharm. Sci., in press.

Signature DUANE G. WENZEL
Director of Project
Professor of Pharmacology

WILLIAM J. ARGERSINGER, JR.
Associate Dean, Graduate School

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Committee:
Dr. Wilson, Chm.
Dr. Jacobson
Dr. Cattell

Cardiovascular, pharmacology and chemistry

#346

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street, New York 17, N. Y.

Application for Research Grant

Date: April 10, 1962

1. Name of Investigator: Anthony A. Albanese, Ph.D.

2. Title: Director, Nutrition and Metabolic Research Division.

3. Institution and Address:

The Winifred Masterson Burke Relief Foundation
The Burke Foundation Rehabilitation Center
White Plains, New York.

4. Project or Subject: The Effect of Nicotine on Protein and Amino Acid Metabolism in Humans.

5. Detailed Plan of Procedure:

It has long been known that when smokers stop smoking there usually occurs a gain in body weight. The report of Professor R. D. Passey on his studies with rats exposed to cigarette smoke shows that cessation of smoke exposure is associated with a return to normal urea nitrogen excretion.

The foregoing observations suggest that it would be fruitful to study in detail the effect of smoking on the nitrogen metabolism of humans. The experience of the Principal Investigator and his associates indicates that changes in the amino acid levels of the blood provide an accurate criterion of protein utilization.[1] To this end, chromatographic methods have been developed which permit

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analysis of amino acid content of blood with samples of 0.1 or 0.2 ml. which are obtained by fingerprick. These procedures have made possible the rapid screening of the effects of various agents (hormones, enzymes, and other substances) on protein and amino acid metabolism.[2, 3, 4, 5]

In applying this experience to the present problem, it is planned to determine the blood amino acid pattern of heavy smokers and non-smokers. Smokers will be asked then to stop for one or two weeks, and determinations of blood amino acid levels will be made during the period of abstention. The interval of abstention may be prolonged or shortened, depending on the findings. In these studies, each subject will serve as his own control which will avoid some of the problems arising from genetic heterogeneity.

In addition to the aforementioned measurements, it is planned to determine also the effects of smoking in terms of the utilization of protein load tests as determined by post-absorptive changes in blood amino acid levels. Professor Passey's report suggests that the pattern of utilization of the load tests may differ between smokers and non-smokers. On the basis of available knowledge, it is expected that the effects of smoking should exhibit themselves primarily with changes in the utilization of the aromatic amino acids.

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It is estimated that the studies outlined will require a year for their completion. If our findings prove promising, it is proposed to extend the investigations with measurements of nitrogen balance in addition to the determination of blood amino acid levels. It is felt that it is of considerable importance to demonstrate the magnitude of the effect of smoking on the storage of nitrogen. Although the amino acid levels provide a good measure of this effect, the need for nitrogen balance data is considered to be acute, since this is generally associated with changes in body weight.

References:

1. Albanese, A. A.: Criteria of Protein Nutrition, in "Protein and Amino Acid Nutrition." (Albanese, Ed.) Academic Press, New York, 1959.

2. Albanese, A. A., Lorenze, E. J., and Orto, L. A.: Nutritional and Metabolic Effects of Some Newer Corticosteroids. N. Y. State J. Med. 61: 3998-4002 (1961).

3. Albanese, A. A., Lorenze, E. J., and Orto, L. A.: Nutritional and Metabolic Effects of Some Newer Steroids. 1. Oxandrolone and Triamcinolone, N. Y. State J. Med. (1962). In Press.

4. Albanese, A. A.: General Nutrition of the Aging Patient with Some Observations on Specific Metabolic Needs, presented as part of a Colloquium on "The Pharmacological Principles of the Aging Patient," Clinical Section of the Gerontological Society, Nov. 10, 1961, Pittsburgh, Penna. Joseph T. Freeman, M. D., Chairman. Also: in "Principles of Drugs in the Elderly," Charles C Thomas Co In Press.

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R: REDACTED MATERIAL

5. Albanese, A. A., Orto, L. A., Thompson, G. F., and Eisenberg, A. Individuality of Protein and Amino Acid Needs. Federation Proc. 21: 403 (1962).

6. Budget Plan:

Salaries:

Supervisory personnel	REDACTED
Research technician	
Test subject fees	
Overhead - 10%	
Total	REDACTED

7. Anticipated duration of work: Two years.

8. Facilities and Staff Available:

The Burke Foundation Rehabilitation Center, registered by the American Medical Association, offers coordinated services based on the philosophy of helping the individual attain maximum physical, psychological, social, and economic functioning.

The laboratory occupies the entire first floor of one of the annex buildings which comprises an area of approximately 3000 square feet, divided into thirteen rooms. It is equipped with the latest apparatus and devices necessary for our type of work. These include: a complete micro Kjeldahl unit, two analytical balances, six centrifuges, six thermostatically controlled ovens, three photoelectric colorimeters, one recording densitometer, two ultraburets, two steam baths, one recording spectrophotometer, one flame photometer, one Aminco portable electrophoresis apparatus one metabolator. In addition, we have a number of home-built units, such as chromatogram

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cabinets and paper electrophoresis apparatus Ample supplies of expendables, such as glassware and chemicals, are on hand

The personnel of the Division is comprised of the Director (Principal Investigator) and his Assistant, an Administrative Assistant, two full-time Research Assistants, and four part-time Research Technologists who are assigned full-time to the Research Program of the Division. Temporary personnel include college students in training for Laboratory Technologists.

9. Additional Requirements:

During the second year of the study, when it is planned to do nitrogen balance as well as blood amino acid level determinations, it is expected that the cost of the researches will be increased due to the additional laboratory time, as well as additional test subjects required. It is estimated that these items will amount to approximately $3,500., making a total cost for the second year of the study approximately $11,000.

10. Additional Information:

The basic body of experience and information relative to the tests and test procedures to be employed in this investigation have been obtained in long-term projects supported by the Office of Naval Research, Air Force, and Sugar Research Foundation. Pertinent publications follow:

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(From Annotated Bibliography of A. A. Albanese)

#121. Metabolic Significance of Blood Amino Nitrogen Levels. A. A. Albanese, L. A. Orto, and D. N. Zavattaro. Federation Proc. 15, 210 (1956). Averages of fasting blood amino N levels of 22 children (5 - 15 yrs.) and 101 adults (40 - 95 yrs.) showed good statistical correlation with the degree of malnutrition expressed in percentage of underweightness. It was found that blood amino N increments 1 hour following oral protein dosages (adults, 0.2 gm/Kg, and children, 0.4 gm/Kg)provided a more accurate criterion of protein nutritional status than fasting amino N levels alone.

#137. Biochemical Significance of Plasma Amino Nitrogen in Man with a Comparison of Other Criteria of Protein Nutrition. A. A. Albanese, L. A. Orto, and D. N. Zavattaro. Metabolism 7, 256-265 (1958). A comparison of the correlation of fasting plasma amino nitrogen levels, plasma amino nitrogen increments with a protein load, blood protein levels and nitrogen balance, with deviations from desirable body weight have been made on some 200 adults. The findings suggest that measurements of plasma amino nitrogen may provide a useful criterion of protein nutrition.

#139. Proteolytic Enzyme Supplements and Protein Utilization in Man. A. A. Albanese, R. A. Higgons, L. A. Orto, and D. N. Zavattaro. Federation Proc. 17, 179 (1958). Studies were undertaken to determine the effect of digestive enzyme administration on the absorption rate of milk proteins in terms of plasma amino nitrogen change. The 13 healthy normal children studied showed no significant change in plasma amino nitrogen index with enzyme administration. Results in 60 adults disclosed that enzyme administration significantly increased the plasma amino nitrogen index of 19 subjects. These increases were most frequently associated with malnutrition and advanced age. Aminograms revealed that positive responses generally included significant increases in essential amino acid content of the blood, especially methionine, threonine and lysine. Chromatographic analyses of in vitro enzyme-milk protein digests indicated that the amino acid pattern changes of the blood in the oral tests could be ascribed to the enzyme supplement.

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#143. Plasma Amino Nitrogen Levels and Protein Needs of Young Children. A. A. Albanese, R. A. Higgons, and L. A. Orto. Federation Proc. 18, 179 (1959). Serial measurements were done for periods of 1 to 25 weeks on 14 infants (2 to 24 months) who had suffered varying degrees of nutritional depletion incident to disease or surgical processes. Results show that decrements in rate of body weight change are accompanied and often forecast by significant decreases in resting plasma amino nitrogen levels. Conversely, increments in rate of body weight change are frequently associated with increasing resting plasma amino nitrogen. Decrements in plasma amino nitrogen and/or body weight followed protein intakes of less than 5.0 gm/kg/day. Adequacy of this level of food intake varied directly with the protein source and prevailing metabolic state of the subjects.

#145. Nutritional Significance of Plasma Amino Acid Levels. A. A. Albanese and L. A. Orto. Scientific Exhibit. Ann. Meeting Fed. Am. Soc. Exper. Biol., Atlantic City, N. J., June, 1959. Copyright 1959. The availability of amino acids was determined from differences in blood levels immediately before and one hour after test meals which supplied proteins and calories in amounts usually consumed by infants and young children Test feedings with a low protein infant formula (1.7 gm.%) were associated with a decrease in plasma lysine as well as total plasma amino nitrogen. Conversely, feedings with conventional whole or evaporated milk formulas were associated with increases in plasma lysine and total plasma amino nitrogen Ingestion of milk or egg proteins (0.25 - 0.50 gm/kg) causes an increase in the lysine content of the blood of young children. Ingestion of cereal or white bread proteins causes a decrease in the lysine concentration of the blood of young children. Supplementation with lysine provides a physiological technique for overcoming the plasma lysine lowering effect of the foods tested. (Copies enclosed)

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Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000

R: REDACTED MATERIAL

Biographical Sketch:

Albanese, Anthony August, Principal Investigator

Born: R

Education: B.S. - New York University 1930
Graduate Work - University of Budapest 1930-32
Ph.D. - Columbia University 1940

Assignments:
Research Assistant - Dept. Pathology, Coll. of P & S, Columbia Univ. 1933-40
Research Associate - Div. of Chem., NIH, 1940-41
Associate in Pediatrics and Research, Johns Hopkins Univ. 1941-45
Assistant Professor of Pediatric Biochemistry, N. Y. Univ. Coll. of Med. 1945-48.
Associate Professor of Pediatric Biochemistry, N. Y Univ. Coll. of Med. 1948-49
Director of Research, St. Luke's Conv. Hospital, 1949-60
Director of Nutrition and Metabolic Research Division, The Burke Foundation 1959--
Director of Geriatric Nutrition Laboratory, Miriam Osborn Memorial Home 1959--

Honorary Positions:
American-Hungarian Exchange Fellow 1930-32
Fellow - Hungarian Ministry of Education. Summers 1931 and 1932
Corn Industries Fellowship 1940-41
Responsible Investigator for Office Scientific Research & Development U.S Gov't. Committee on Med. Research 1941-45
Responsible Investigator for Office of Naval Research 1945--
Responsible Investigator for Air Research and Dev. Command 1960--
Associate Editor, N. Y. State Journal of Medicine 1959--

Special Societies:

REDACTED

REDACTED

Publications:
164 publications in the field of human nutritional research and methods are contained in 5 books

Certifications:
Specialist in Human Nutrition, Am. Board of Nutrition
Diplomate Mexican Gerontological Society and Mexican Society of Geriatrics 1956 (Honorary)

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Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000

Signature Antony R. Albanese
Director of Project

George Bunch
Business Officer of the Institution

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EPIDEMIOLOGY, STATISTICS and PSYCHOSOMATIC NO. 347

COMMITTEE:
Dr. Wilson, Chm.
Dr. Cattell
Dr. Jacobson
(Dr. Little)

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

APPLICATION FOR RESEARCH GRANT

Date: April 12, 1962

1003542899

1. Name of Investigator: ARNOLD R. KAPLAN, PH.D.

2. Title: Director, Laboratory of Medical Genetics
Cleveland Psychiatric Institute and Hospital

3. Institution and Address: Psychiatric Research Foundation of Cleveland
1708 Aiken Avenue
Cleveland 9, Ohio
(Executive Director: Edward N. Hinko, M. D.)

4. Project or Subject: EXAMINATION OF CORRELATIONS BETWEEN TASTE THRESHOLDS (for QUININE and 6-n-propylthiouracil) and HABITUAL (i.e., smoking), PHYSIOLOGICAL and PATHOLOGICAL VARIABLES.

5. Detailed plan of procedure:

A. SPECIFIC AIMS: - The specific aims of the proposed research project include clarification of the constitutional basis and significance of correlations occurring between taste threshold categories, as defined for quinine and 6-n-propylthiouracil, and the following variables:

(1) habitual -- i. e., smoking habits;
(2) physiological -- i. e., metabolic rates, blood pepsinogen levels;
(3) pathological predispositions -- i. e., to gastritis, gastric ulcer, duodenal ulcer, coronary disease, thyroid disease, migraine, etc.

B. METHODOLOGY: - Taste thresholds will be determined in all subjects for quinine sulfate (U.S.P. crystals, Mallinkrodt) and 6-n-propylthiouracil (Nutritional Biochemical Corp.). Normal subjects and patients in the relevant pathological categories will be tested with a modification of the Harris-Kalmus double-blank placebo procedure and final sorting-out technique. The basic method involves 20 concentrations (ranging from 3.66×10^{-7} to 3.84×10^{-1}) each of which is double the concentration of the next-lower solution. Previously-published studies of taste threshold have been based on defective methodology. The following refinements now make possible an accurate genetic study of the taste threshold phenomena:

(1) Threshold determinations to fractional powers of 0.1. We are now utilizing

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a refinement of the Harris-Kalmus procedure which involves not only doubling concentrations, but also fractional powers of the 0.1. between the primary concentrations. Our technique involves, therefor, determination of taste threshold to an accuracy of one decimal point beyond that employed in the original Harris-Kalmus procedure. This refinement is important because certain thresholds, and certain combinations of 6-n-propylthiouracil thresholds and quinine thresholds, are apparently genetic entities. The genetic mechanisms involved can only be elucidated, however, if the more exact thresholds are determined. For example, with an unrefined Harris-Kalmus procedure, a subject with an actual threshold of '12.3' would be categorized as '13.' Since the threshold range between '12' and '13' appears to include a critical dichotomy between genetic entities, the previously-used techniques are unsuitable for accurate genetic determinations.

(2) Previous use of phenylthiourea ('P.T.C.') instead of 6-n-propylthiouracil meant that taste measurements were based on a very odorous and toxic compound -- and the apparent distributions of taste threshold categories were distorted by the uncontrolled variable of differential olfactory sensitivities to the compound. Thus, previous studies (e. g., by Merton) included mating pairs of 'nontasters' who produced 'taster' offspring -- in contradiction to the classical genetic hypothesis that the factor for 'nontaster' is transmitted as a simple Mendelian recessive. The use of 6-n-propylthiouracil is also justified by its superior potency, which facilitates more reliable differentiation between the different threshold categories; and by the fact that 6-n-propylthiouracil is the least toxic of the thioureas.

(3) Sequence in determination of the taste thresholds. Leguebe and Kalmus each tested the taste thresholds for phenylthiourea and quinine, in that consecutive order. We have found that the occurrence of a strong affinity for the thiourea compound blunts, for several hours, the taste thresholds for subsequently-tested compounds. Only a testing sequence in which the quinine threshold is determined first and the thiourea (in our procedure, 6-n-propylthiouracil) afterwards, provides accurate threshold determinations for both compounds.

Smoking data will be based on the standard questionaire of the Tobacco Industry Research Committee. The utilization of the standard questionaire will facilitate replication by other investigators.

Blood pepsinogen levels will be determined by standard procedures, and correlated with the other variables being investigated. Mirsky et al. have shown that patients with duodenal ulcer histories have high blood pepsinogen levels compared to the general population. Our preliminary findings of correlations between taste insensitivity (i. e., high threshold), ulcer history and other variables, suggest the possibility of an etiological relationship between the taste-thresholds (and relevant genetic factors) and blood pepsinogen levels.

Data relevant to body type will also be evaluated. We will determine heights and weights of the subjects -- two easily-accessible categories of data, from which the subjects' body surfaces may be calculated. Body surface, rather than 'Sheldonian' or 'Kretchmerian' categories, is related to metabolic rate -- and this data will be investigated for correlations with the above variables. The importance of considering metabolic rate (indirectly, from body surface calculations) is indicated by the data which indicate a correlation between taste threshold and thyroid activity. We have found that hyperthyroid patients tend to be insensitive tasters -- i. e., nine of the subjects in a pilot group of 12 tested hyperthyroid patients could not taste even the uppermost concentrations of quinine and 6-n-propylthiouracil. Since the latter substance is an antithyroid drug, and hyperthyroid patients (with diagnoses of thyrotoxicosis or toxic nodular goiter) cannot taste the saturated solution of an antithyroid drug, taste threshold for this drug is related to metabolic rate. A significantly higher proportion of insensitive ("non-") tasters has been found in hyperthyroid subjects than in the general population. These observations gain

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significance when considered in the light of data reported by Kitchen et al., who observed a tendency to "taste blindness" (i. e., insensitivity) in patients with multi-adematous goitre, both toxic and non-toxic, and in those with toxic diffuse goitre; and data reported by Shepard and Gartler, on parents of cretins, which indicate a similar correlation between taste sensitivity and thyroid activity. Based on the above observations, we would expect to find positive correlations, on the one hand, between high thyroid activity, taster insensitivity and heavy smoking -- and, on the other hand, between low thyroid activity, taster sensitivity and non-smoking. The pathologies of which predispositions are correlated with taste insensitivity may be primarily related to metabolic variables, as may be the variables of taste sensitivity and smoking habits.

C. PREVIOUS FINDINGS AND OTHER RELEVANT MATERIAL: - Preliminary pilot studies indicate that subjects who are extremely insensitive to taste for 6-n-propylthiouracil ('threshold levels 13-14') always fall in the range of low taste sensitivity for quinine ('threshold levels of 7 and above'), and include a significantly high proportion of individuals with positive histories for gastritis, ulcers and migraine. Our studies have also shown that drug reactivity (i.e., drug sensitivity) is correlated with taste thresholds for quinine and 6-n-propylthiouracil -- as are food dislikes and smoking habits. Therefor, we consider it reasonable to examine the genetic factors relevant to constitutional differences correlated with the above variables. To date, there has been no 'clean-cut' study of the genetics of taste thresholds for 6-n-propylthiouracil and the relevant involvement of taste thresholds for quinine.

Krut, Perrin and Bronte-Stewart recently reported finding a significant correlation between smoking habits and high taste thresholds for quinine. They found that only the taste threshold for the bitter compound is correlated with smoking habits -- and that taste thresholds for sweetness, saltiness and acidity have no correlations with smoking habits. Our own data indicate that smoking habits and food dislikes are both apparently related to taste thresholds for the bitter compounds (only). Our investigations confirm the above observations reported by Krut et al. -- whose methodology, incidentally, involved placement of a drop of test solution with a pipette on the middle of the tongue. They tested for taste thresholds for phenylthiourea as well as for quinine, but found no correlation with the former. Their technique (of placing one drop of phenylthiourea solution in the middle of the tongue) does not facilitate taste detection in many cases, however, and the methodology is defective for determination of phenylthiourea taste threshold. Two or three seconds of lag time are required for tasting phenylthiourea -- and in addition, for taste detection, the solution must flow all over the tongue and especially over the root and sides. Their studies of taste thresholds for phenylthiourea are meaningless due to the methodological defects, but their studies with quinine provided accurate and reproducable results -- because taste testing for quinine does not require lag time and does not require contact on the deep portion of the tongue. We have preliminary evidence (based on 137 healthy subjects) which support the findings of Krut et al. that 'sensitive tasters' contain significantly lower proportions of 'heavy smokers' than do the relatively 'insensitive tasters.' Preliminary data also indicate correlations between taste thresholds (for quinine and 6-n-propylthiouracil) and morbidity rates for several pathologies. A positive correlation has also been found between high taste sensitivity (i.e., low taste threshold) for the bitter compounds and extent of food dislikes. No correlations have been found with taste thresholds for sweetness, saltiness and acid.

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D. REFERENCES

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Krut, L. H., M. J. Perrin and B. Bronte-Stewart. 1961. Brit. Med. J., 1;384.
Leguebe, A. 1960. Bull. Inst. Royal des Sciences Nat. de Belgique, 36:1.
Merton, B. B. 1958. Acta Genet. Statist. Med., 8:114.
Shepard, T. H. and S. M. Gartler. 1960. Science, 131:929.

6. Budget Plan: (First Year)

a.	Salaries	$6,600.00
b.	Expendable Supplies	1,500.00
c.	Permanent Equipment	1,190.00
d.	Overhead (15% of a,b,e)	1,552.00
e.	Other	2,250.00
	TOTAL	$13,092.00

7. Anticipated Duration of Work: THREE YEARS
(See 'Additional Requirements' for suggested second and third year budgets).

8. Facilities and Staff Available: The principle investigators are Dr. Arnold R. Kaplan, Director of the Laboratory of Medical Genetics, and Mrs. Mary Wilkinson Fox, Statistics Consultant and Research Associate, at the Cleveland Psychiatric Institute and Hospital; Dr. Roland Fischer, Senior Research Biochemist, and Mrs. Frances Griffin, Research Associate, at the Columbus Psychiatric Institute, and Ohio State University Medical School. Facilities available include the research and clinical facilities of the respective institutions. Agreements for collaboration have been made with the chiefs and staff members of the Departments of Psychiatry, Psychosomatic Medicine, Medicine, Pharmacology and Physiological Chemistry at the Ohio State University Medical School -- and with the director of the serology laboratory at the Cleveland Metropolitan General Hospital.

9. Additional Requirements: Budget Plan - Second Year and Third Year.

		Second Year	Third Year
a.		$6,700.00	$6,800.00
b.		500.00	400.00
c.		150.00	- -
d.		1,357.00	1,290.00
e.		1,850.00	1,400.00
	TOTALS	$10,557.00	9,890.00

10. Additional Information (including relation of work to other projects and other sources of supply)

The named applicant investigators are staff members of their respective (state) institutions and draw full-time salaries therefrom.

Other projects, in progress and planned (and for which some pilot data have already been collected) which are related to the present proposal are as follows:

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10. Additional Information -(Cont'd)

(1) We are planning a concomitant study to test the possibility that certain personality types, as defined by quantifiable personality tests, may be correlated with certain thresholds and/or threshold combinations for tasting 6-n-propylthiouracil and quinine. If the pilot studies should yield significant data, we would include the personality tests in the present project.

(2) In conjunction with the above study, we are planning to investigate the occurrence of possible personality correlates with the dichotomy separating subjects into categories of 'learners' and 'nonlearners' of greater taste sensitivity.

(3) Studies are continuing, investigating the relationship between drug (psilocybin) reactivity of 'normal' subjects as related to taste thresholds for quinine and 6-n-propylthiouracil.

(4) Studies are continuing, investigating the relationship between taste threshold for quinine and 6-n-propylthiouracil in uncategorized mental patients and the setting-in of Parkinsonism with progressively-increased chlorpromazine dosages.

(5) Studies are planned to determine genetic linkage between the loci for the 'taster' factor, blood types and other genetic markers.

(6) Studies are planned, to investigate the taste threshold phenomena in twin-family pedigrees.

Signature ARNOLD R. KAPLAN
Director of Project

EDMOND N. HINKER, M. D.
Business Officer of Institution

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CARDIOVASCULAR, PHARMACOLOGY AND CHEMISTRY

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street New York 17, N. Y.

#348

DR. JACOBSON-CHM.
DR. CATTELL
DR. BING

Application for Research Grant

Date: April 20, 1962

1. Name of Investigators: Ernest C. Griesemer, William G. Clark, and Eskil A. Hansson.

2. Titles: Clin. Asst. Professor, Dept. Pharmacology; Clin. Assoc. Prof., Dept. Physiological Chemistry; Asst. Res. Physiological Chemist.

3. Institution & Address: Medical Center, University of California Los Angeles 24

4. Project or Subject: Effect of Nicotine and Related Substances on Amine Levels in the Nervous System.

5. Detailed Plan of Procedure:

It is the purpose of this investigation to study the effect of nicotine and its congeners and metabolites on the uptake, binding, storage and release of norepinephrine and dopamine in the nervous system and some of its target organs, with emphasis on the brain. Earlier investigators have shown that nicotine liberates catechol amines from the adrenal medulla, heart and blood vessels (Tainter, 1926; Wada, et al., 1938; Watts, 1960; Burn, et al., 1959; Burn, 1960). There are good reasons to believe that these amines are neurohumoral transmitters or modulators, and it is quite possible that one cause of the pleasure of smoking may be due to the release of these amines from their binding sites in the brain. In earlier studies by one of us (Hansson and Schmiterlöw, 1961, 1962; Appelgren, et al., 1962; Schmiterlöw and Hansson, 1962) it was found that the brain and adrenal medulla very rapidly concentrate radioactive nicotine &/or its metabolites when injected parenterally. Initially it is concentrated in the nerve cell rich parts of the brain. Schievelbein, et al. (1961, 1962) recently demonstrated that nicotine releases serotonin from intestine and brain and also releases histamine from blood platelets and mast cells. They found in human subjects an increased urinary excretion of 5-hydroxyindoleacetic acid caused by smoking 5-10 cigarettes. They invoke this serotonin release in the psychic effect of smoking.

Our previous work on the uptake by brain of radioactive nicotine can be illustrated by the radioautographs of sagital sections of rat whole body and brain shown in Figures 1 and 2.

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(Insert Figs. 1 & 2 here)

It is our hope that knowledge about the effect of different doses of nicotine and particularly its congeners, analogues, and metabolites, on brain catechol amines will in part clarify the psychopharmacological effect of smoking.

Technique: Nicotine and its analogues will be administered to rats and mice at different doses and the animals sacrificed at different times after the injections. The brains, heart, sympathetic ganglia, and spleens will be removed, and analyzed for dopamine, noradrenaline and serotonin by modifications of methods described by Shore and Olin (1958), Kuntzman, et al., (1961), Carlsson and Waldeck (1958), Murphy and Sourkes (1962) and Towne, et al., (1962), with which we have had considerable experience. Moreover, it is hoped to study the uptake, storage and release of radioactive norepinephrine, dopa, dopamine and serotonin and their amino acid precursors in different parts of the brain as affected by nicotine and its congeners, using techniques described by Axelrod, et al., (1961), Udenfriend, et al., (1961), Hess, et al., (1961), Hertting, et al., (1961), and Dengler et al., (1961).

References

Appelgren, L.E., Hansson, E., & Schmiterlöw, C.G., "The Accumulation and Metabolism of C^{14}-labeled nicotine in the brain of mice and rats." Acta Physiol. Scand., 1962 (in press).

Axelrod, J., Hertting, G., & Patrick, R.W., J. Pharmacol. Exp. Therap. 134: 325, 1961.

Burn, J.H., & Rand, M.J., Brit. Med. J. 1: 903, 1958.

Carlsson, A. & Waldeck, B., Acta Physiol. Scand. 44: 293, 1958.

Dengler, H.J., Speigel, H.E., & Titus, E.O., Science 133: 1072, 1961.

Hansson, E. & Schmiterlöw, C.G., "Physiological Disposition and Fate of C^{14}-labeled nicotine in Mice and Rats." J. Pharmacol. Exp. Therap., 1962 (in press).

Hertting, G., Axelrod, J., Whitby, L.G., ibid., 134: 146, 1961

Hess, S.M., Connamacher, R.H., Ozaki, M., & Udenfriend, S., ibid., 134: 129, 1961.

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Murphy, G.F. & Sourkes, T.L., in Quastel, J.H. (Ed.), Methods in Med. Res., 9: 379, 1960.

Schievelbein, H., Werle, E., & Jacoby, W., Naturwiss. 48: 603, 1961.

Schievelbein, H., & Werle, E., Psychopharmacologia 3: 35, 1962.

Schmiterlöw, C.G., & Hansson, E., "Physiological Disposition and Fate of C^{14}-labeled Nicotine in Mice." Nature, 1962 (in press).

Shore, P.A., & Olin, J.S., J. Pharmacol. Exp. Therap. 122: 295, 1958.

Tainter, M.L., ibid., 27: 201, 1926.

Towne, J.C., Sherman, J., & Schaefer, T., Fed. Proc. 21: 420, 1962.

Udenfriend, S., Connamacher, R., & Hess, S.M., Biochem. Pharmacol. 8: 419, 1961.

Wada, M., Hirano, T., & Tiba, M., Tohoku J. Exp. Med. 33: 189, 1938.

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6. Budget Plan:

a. Salaries:	Laboratory Technician, Grade I	$ 5,028.00	
	Laboratory Assistant, Grade I	4,140.00	
	Sr. Typist Clerk(25% FTE)*	1,035.00	
	Retirement Contributions (10%)	1,020.00	$11,223.00
b. Expendable Supplies:	Glassware ($500.), Chemicals (1,200.) Animals and Animal Care ($800.)		2,500.00
c. Permanent Equipment:	Rotary Evaporator Mixer and accessories(Buchler) $500. Virtus Homogenizer and acces. ($500.00)		1,000.00
d. Overhead at 15% of a, b, & E			2,197.00
e. Other:	1. Publication and Reprint Costs	$ 104.25	
	2. Travel to 1 national meeting	800.00	904.25
	TOTAL:		17,824.25

* Mandatory policy of UCLA Department of Pharmacology for providing assistance to defray departmental administrative cost in handling grants.

7. Anticipated Duration of Work: July 1, 1962 to June 30, 1963.

8. Facilities and Staff Available:

A. Facilities: Psychopharmacology Research Center, Veterans Administration Hospital, Sepulveda, Calif. (W.G. Clark, Director), containing 15 labs., including neurochemistry, neuropharmacology, radioisotopes, enzyme preparation room, vivarium, etc.

B. Staff: (1) Griesemer, Ernest C. B.S. Loyola Univ., Chicago, 1950; Ph.D., Northwestern Univ. 1955; Asst. Pharmacol., Loyola Univ. 1950-1, Res. Fellow 1951-2; Asst. Pharmacol., Northwestern Univ., 1956-61; Pharmacologist, V.A. Hosp. Sepulveda, 1961 - ; Clin. Asst. Prof., Pharmacol. Med. Center, Univ. Calif., Los Angeles, 1962 - . Nine Publications.

(2) Hansson, Eskil A. DVM Doznet, Kungl. Veterinarhogskolan, Stockholm 1959; Asst. Pharmacol., ibid. 1954-9; Asst. Prof., ibid, 1959 -; Asst. Res. Physiol. Chemist (Am. Cancer Soc. and Fulbright Fellowships), Med. Center, Univ. Calif, Los Angeles, 1962 - . Twenty-five publications.

(3) Clark, William G. (See WMo's Who in the West" 7: 135, 1960; Amer. Men. Sci. 10th Ed.,Phys. and Biol. Sci.: 685, 1960). A.B. Univ. Texas, 1931; Ph.D. Calif. Inst. Tech. 1937; Lab. and Res. Asst. U. Texas (E.J. Lund), 1927-32; Teaching Fellow and Lab. Asst., Caltech; 1933-7; Research

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Assoc. Biochem., Scripps Inst. Oceanography, 1937-8; Res. Assoc., Scripps Metabolic Clinic, 1938-9 & 1947-9; Instr.; Zool., U. Minn., 1939-41; Asst. Prof., 1941-4; Assoc. Prof. Physiol. & Av. Med., U. So. Calif., 1944-6; Fowler Res. Fellow in Pharmacology, U. So. Calif., 1946-7; Chief, Physiol.-Pharmacol., V.A. Center, Los Angeles, 1949-1960; Director, Psychopharmacology Res. Labs., V.A. Hosp., Sepulveda, Calif., 1960- ; Clin. Assoc. Prof., Physiol. Chem., Med. Ctr., U. Calif., Los Angeles, 1949- ; Consultant, Psychiatry, ibid., 1956-.

Societies: Am. Chem. Soc., Soc. Exp. Biol. & Med. (Pres. So. Calif. Sect. 1951), Am. Physiol. Soc., Am. Soc. Pharmacol. Exp. Therap., W. Soc. Clin. Res., N. Y. Acad. Sci. (Fellow), S. Calif. Biochem. Soc. (Pres. 1951), W. Pharmacol. Soc., Am. Fed. Clin. Res., Am. Therap. Soc., Am. Assoc. U. Prof., AAAS (Fellow), Sigma Xi; Editorial Advisory Board, "Current Contents", Member Bd. of Dir. of L. A. Com. on Alcoholism, V. A. Nat'l Com. on Basic Sci. Res.; VA Nat'l Program Com. on Neuropsychiatric Res. 137 publications; 40 since 1955.

9. Additional Requirements: None.

10. Additional Information (Including relation of work to other projects and other sources of supply): None.

Signature _____
Director of Project

_____
Responsible Administrative Officer

_____
Business Officer of the Institution

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BIOASSAY, CARCINOGENESIS and TISSUE CULTURE # 349

COMMITTEE:
Dr. Kotin, Chm.
Dr. Jacobson
Dr. Reimann
(Dr. Little)

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

APPLICATION FOR RESEARCH GRANT

DATE: April 18, 1962

1. Name of Investigator: ARTHUR FURST, PH.D.

2. Title: Director

3. Institution and Address: Institute of Chemical Biology
University of San Francisco
San Francisco 17, California

4. Project or Subject: "A CONTROLLED STUDY IS PROPOSED TO EVALUATE THE EFFECT OF ADMINISTRATION OF TRACE METALS (WITH OR WITHOUT EXPOSURE TO CIGARETTE SMOKE) ON THE INCIDENCE OF PULMONARY ADENOMAS IN STRAIN A MICE."

1003542908

5. Detailed Plan of Procedure:

Background to problem:

The highly inbred Strain A albino mice developed by Strong (J. Hered. 27, 21-24 (1926) is an excellent test animal for the study of primary tumors of the lung. The spontaneous incidence of these pulmonary tumors is well documented by Bittner (Pub. Health Rep. 54, 380-392 (1939) and Andervort (Pub. Health Rep. 52, 212-221 (1937) and J. Nat. Cancer Inst. 1, 225-239 (1940). Adequate statistical studies have also been published on these tumors.

Following some reports by Cogbill and Hobbs on the nickel content of cigarettes (Tobacco Sci. 1, 68-73 (1957), the Sundermans implicated nickel in tobacco as being carcinogenic. They reasoned that each cigarette contained 2 µg of Ni; the main stream smoke contains 2% to 7% CO. From these data they postulate that if Ni $(CO)_4$ can be formed, the amount inhaled by man would be three times that which is carcinogenic to rats (Am. J. Clin. Path. 35, 203-209 (1961).

The Proposal:

A study is proposed to evaluate the effect of nickel compounds on the incidence of spontaneous pulmonary adenomas in Strain A mice. Spectroscopically analyzed nickel (ous) acetate, or nickel chloride will be adminstered IP, or in the drinking water, or as an atomized spray to different groups of mice of

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same age and weight. Equal numbers of males and females will be used. The dosages will be calculated so that each group receives the same amount of nickel, and this value will be at least 100x reported found in cigarettes. Time of exposure will vary. One set of controls will get vehicle alone; a second set will get urethane solution. A third set of controls will get IP, or in the drinking water, a urethane-nickel complex solution. All dates will be analyzed statistically.

A method will be devised to analyze for nickel in lung tissue, both normal and malignant. The most sensitive reagent for nickel, 2, 3-quinoxalinedithiol, was developed at the University of San Francisco (Morrison and Furst, J. Org. Chem. 21, 470 (1956) and was adapted for inorganic quantitative analysis (Skoog, Lai and Furst, Anal. Chem. 30, 365 (1958).

The information obtained would help elucidate the role of nickel in the pathogenesis of lung tumors in Strain A mice.

Future:

After the first phase is completed in about one year, a conference would be requested with members of the Research Committee. If as a result of this discussion it is concluded that the study should be continued, the experiments would be repeated adding exposure to cigarette smoke as a new variable.

6. Budget Plan:

a.	Salaries	$5,000.00
b.	Expendable Supplies (mice, chemicals)	1,000.00
c.	Permanent Equipment	--
d.	Overhead (15% of a,b,e)	960.00
e.	Other (travel to meeting)	400.00
	TOTAL	$7,360.00

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7. Anticipated Duration of Work: First phase - One year
Second phase - Two additional years

8. Facilities and Staff Available: Complete facilities are available for study of the first phase. The Institute has the major equipment, including automatic spectrophotometers.

9. Additional Requirements: If second phase will be done, it will be necessary to acquire four smoking machines to be purchased from Mt. Zion Hospital (at $1,000) and a microscope. The addition of one diener will also be necessary. Total for the second year's budget will be $12,000, and $10,500 for the third year.

10. Additional information (including relation of work to other projects and other sources of supply)
A proposal has been submitted to the NIH for a study of the effect of trace metals on the carcinogenicity of azo dyes. These projects would complement each other.

Signature ARTHUR FURST
Director of Project

JAMES M. CORBETT, SEC'Y-TREAS.
Business Officer

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MISCELLANEOUS #350

COMMITTEE:
Dr. Jacobson
Dr. Lynch
Dr. Cattell
(Dr. Parmele)

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

APPLICATION FOR RESEARCH GRANT

Date: April 26, 1962

1. Name of Investigator: PAUL G. MAHLBERG, PH.D.

2. Title: Assistant Professor in Botany

3. Institution & Address: Biological Sciences
University of Pittsburgh
Pittsburgh 13, Pennsylvania

4. Subject: "NICOTINE CONTENT IN ALBINO AND GREEN GENETIC STRAINS OF NICOTIANA TABACUM L. IN TISSUE CULTURE".

1003542910

5. Detailed Plan of Procedure: Rate of nicotine production is interpreted to be an inherited trait controlled by specific gene locus under which conditions high nicotine content is dominant over low nicotine content (Valleau, 1949).

In this study highly isogenic strains of known genic composition for the trait of albinism and chlorophyll pigmentation will be analyzed for nicotine content. Comparative analyses will be made upon normal plants of each strain and abnormally proliferated callus derived from these strains. The data will ascertain: 1) if the gene loci under study are associated with nicotine production in the normal plant; and 2) if gene mutations can occur in proliferated callus leading to altered rates of nicotine production in the strains.

Genetic strains of N. tabacum possessing the Mendelian character of albinism in the ratio of: one homozygous green; two heterozygous green; and one homozygous albino have been established in tissue culture. In addition another strain, Cuba White, also has been developed in culture. Albinism in tobacco is controlled by duplicate factors designated Ws_1 located on the G chromosome and Ws_2 located on the T chromosome. The genetic composition of the above isogenic strains relative to pigmentation is: a) albino, $ws_1ws_1ws_2Ws_2$; b) heterozygote, $ws_1ws_1ws_2ws_2$; c) homozygote, $ws_1ws_1Ws_2Ws_2$ and d) Cuba White, $Ws_1Ws_1Ws_2Ws2$. These related strains differ by a single, one pair or two pairs of genes. Plants of these strains will be cultured under sterile conditions to produce normal plants or proliferated callus masses (Venketeswaran and Mahlberg, 1962). The basal culture medium will include (mg/l): NH_4NO_3, 800; $Ca(NO_3)_2.4H_2O$,100; KNO_3,80; KCI,65; KH_2PO_4, 300; $MgSO_4.7H_2O$, 35; $ZnSO_4.7H_2O$,0.1; H_3BO_3,0.1; $MnSO_4.H_2O$,0.01; $CuSO_4.5H_2O$,0.003; $ALCl_3$,0.003; $NiCl_2.6H_2O$,0.003;Kl,0.001; $FeCl_3.6H_2O$,0.1; sucrose, 30,000. The medium is solidified with 7 gm./liter Difco

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agar and adjusted to a pH of 5.5. The above medium is supplemented as follows (per liter) for induction of proliferation: 2,4-dichlorophenoxyacetic acid, 1 x 10^{-6}M (2,4-D), indole-3-acetic acid, 1 x 10^{-6}M (IAA) and yeast extract, 1 gm. (Y.E.). The cultures will be maintained in a culture room at 25 ± 1°C. with illumination for 12 hours a day with fluorescent lamps. The cultures of normal plants and the proliferated callus tissues derived from the different strains will be analyzed for nicotine content employing the techniques of Dawson (1953).

This investigation can provide data on the relative levels of alkaloid production in the several genetic strains. A primary point of interest in this study will be to determine whether nicotine production will remain constant in the several strains of abnormally proliferated callus tissues over a period of time.

In a potential future extension of this study, it may be possible to analyze chemical factors which will permanently alter the genic composition of callus cells resulting in lowered alkaloid production. It then will be of interest to determine if the plants induced to form from such callus, employing techniques now at our disposal, will retain the depressed level of alkaloid production.

6. Budget Plan:

a.	Salaries	$7,738.00
b.	Expendable Supplies	362.00
c.	Permanent Equipment	---
d.	Overhead (15% of a,b,e)	1,245.00
e.	Other (Travel)	200.00
	TOTAL	$9,545.00

7. Anticipated Duration of Work: September 1, 1962 - August 31, 1963.

8. Facilities and Staff Available: Culture facilities and equipment are available. I shall secure a research assistant to assist in this project.

9. Additional Requirements: ------

10. Additional Information (including relation of work to other projects and other sources of supply):

The present proposal is a result of techniques whereby strains of tobacco can be successfully established in tissue culture. The initial studies have been prepared for publication (Venketeswaran and Mahlberg, 1962).

Recently I have accepted an invitation to join the faculty of the Botany Department at the University of California (Berkeley) for a nine-month period. I plan to carry out this program while at Berkeley as well as at the University of Pittsburgh.

Currently I am receiving support from the National Institutes of Health (Cancer Institute) grant number C-5714, entitled, "Growth rate analysis of suspended plant cell cultures", in which the cells isolated from callus tissues are being evaluated for morphogenetic potentialities; and, an Institutional Grant from the American Cancer Society, entitled, "Cine-phase observations upon growth phenomena of isolated plant cells", in which the response of single cells subjected to diverse cultural conditions are being analyzed cinemicrographically.

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Dawson, R. F. Alkaloid biogenesis. IV. The non-availability of nicotinic acid-carboxyl-C^{14} and its ethyl ester for nicotine biosynthesis. Jour. Amer. Chem. Soc. 75: 1953.

Mahlberg, P. G. Isolation of a floating cell strain from submerged cell cultures pf Euphorbia marginata. Exp. Cell Res. 26: 1962.

Mahlberg, P. G. and S. Venketeswaran. Phase cinemicrographic observations on cultured cells.

Signature PAUL G. MAHLBERG
Director of Project

MAX A. LAUFFER
Business Officer of the Institution

1003542912

Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000

CARDIOVASCULAR, PHARMACOLOGY and CHEMISTRY

#351
Compare: #4A

Activated: 1/1/56
Renewed: 1/1/57
Renewed: 1/1/58
Renewed: 1/1/59

COMMITTEE:
Dr. Jacobson, Chm.
Dr. Kotin
Dr. Cattell

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

APPLICATION FOR RESEARCH GRANT

Date: April 20, 1962

1. Name of Investigator: SIMON H. WENDER, Ph.D.

2. Title: Studies on Polyphenols of Cigarette Smoke

3. Institution & Address: University of Oklahoma Research Institute
Office of Executive Director
Norman, Oklahoma

1003542913

4. Project or Subject: On this project, we shall undertake the identification of individual polyphenolic compounds present in the smoke from cigarettes and the preparation, where feasible, of these compounds for studies on their metabolism and possible effect on human health.

5. Detailed Plan of Procedure:

Our present studies on cigarette smoke will be expanded in an effort to isolate and identify the many individual polyphenols present. These include the large group of phenolic acids that our laboratory was the first to discover as being present in cigarette smoke and also still another group of compounds recently discovered in cigarette smoke in our laboratory, and as yet not reported. The latter apparently contains aromatic aldehydes. No previous report on either group has appeared in the literature.

Extensive paper and column chromatography, infrared and ultraviolet spectrophotometry, and spectrophotofluorimetry will be utilized.

Certain polyphenols, such as rutin and chlorogenic acid, are known to be present in relatively larger amounts in cigarette tobacco. In such cases, dry samples of each will be heated strongly, and the resulting substances will be analyzed for possible clues as to what their breakdown products might be in cigarette smoke. We have initiated such studies in our laboratory with very promising preliminary results.

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Procedures for synthesizing sufficiently large amounts of a polyphenol for biological studies will be developed, where literature reports have indicated possible effects of such a compound on animal health. In some cases, it is anticipated that such polyphenolic compounds may be synthesized to contain a specifically labeled atom such as carbon 14, in order to investigate more effectively the fate of these compounds in the smoke from cigarettes, and also their biological pathway. And if T.I.R.C. so suggested, such compounds could be studied biologically in cooperation with workers at the University of Oklahoma School of Medicine. Research on the synthesis of radioactive scopoletin is definitely to be done.

PREVIOUS WORK

Wender and co-workers have purified and identified quinide (gamma lactone of quinic acid) and also quinic acid on paper chromatograms of extracts of mainstream cigarette smoke (Journal of Organic Chemistry, 26, 3017 (1961). Also, Wender's group has identified esculetin (6,7-dihydroxycoumarin) (J. Org. Chem. 24, 1134 (1959), scopoletin (6-methoxy-7-hydroxycoumarin) (J. Org. Chem. 23, 204 (1958), and cis - and trans - caffeic acids (J. Org. Chem. 25, 658 (1960) in the mainstream smoke from cigarettes. Quantitative methods for the determination of scopoletin in tobacco smoke and in tobacco products have been developed by these University of Oklahoma scientists (Anal. Chem. 30, 2041 (1958)).

In cooperation with Mr. Marvin Shetlar of the University of Oklahoma School of Medicine and students, studies have been undertaken on the fate of esculetin, scopoletin, and quercetin (3,3', 4',5,7-pentahydroxyflavone) in the laboratory rat (Arch. Biochem. and Biophys. 75, 538 (1958); 81, 430 (1959); 85, 264 (1959); and Biochim. et Biophys. Acta. 44, 606 (1960)).

An improved synthesis of scopoletin has been devised (Biochim. et Biophys. Acta. 44, 163 (1960).

Although no other laboratory has reported the identification of any polyphenolic acids in cigarette smoke, Yang and Wender have recently identified twelve phenolic acids in cigarette smoke (Journal of Chromatography, in press). They are m-hydroxybenzoic, p-hydroxybenzoic, protocatechute, vanillic, syringic, o-hydroxyphenylacetic, p-hydroxphenylacetic, m-hydroxyphenylacetic, cis- and trans-p-coumaric, cis-and trans-ferulic, m-hydroxyphenylpropionic, and p-hydroxyphenylpropionic acids.

6. Budget Plan:

(One Ph.D. full-time plus one M.S. or Ph.D. part-time)

a.	Salaries	$11,800.00
b.	Expendable Supplies	1,100.00
c.	Permanent Equipment	None
d.	Overhead (15% of a,b,e)	2,060.00
e.	Other*	850.00
	TOTAL	15,810.00

*O.A.S.I., reprints, travel, fringe benefits when applicable.

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7. Anticipated Duration of Work: THREE (3) Years

8. Facilities and Staff Available: Adequate research facilities for the proper prosecution of the investigation are available.

Dr. Chao-Hwa Yang, who isolated and identified the phenolic acids, scopoletin, etc. in cigarette smoke, is available for the full-time Ph.D. position. Mr. Alex Zane, M. S. in Chemistry, is now working part-time on the pyrolysis products of rutin, and should be available for the other position.

9. Additional Requirements: NONE

10. Additional Information (Including relation of work to other projects and other sources of supply):

Similar research on the polyphenols in cigarette smoke has been supported by the National Institutes of Health for the past three years ($55,168). The N. I. H. project expires August 31, 1962. Prior to that, support was kindly furnished by the Tobacco Industry Research Committee.

Signature SIMON H. WENDER
Director of Project

CHARLES S. STANDLEY
Business Officer of Institution

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PATHOLOGIC - DIAGNOSTIC

#352

COMMITTEE:
Dr. Reimann, Chmn.
Dr. Rienhoff
Dr. Lynch
Dr. Kotin

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

APPLICATION FOR RESEARCH GRANT

Date: MARCH 9, 1962

1. Name of Investigator: WILLIAM M. TUTTLE, M. D.

2. Title: SURGEON

3. Institution & Address: Harper Hospital
3825 Brush Street
Detroit 1, Michigan

4. Project or Subject: STUDY OF ROUNDED PULMONARY CARCINOMAS

5. Detailed Plan of Procedure:

It has long been noted that rounded pulmonary carcinomas arising in the periphery of the lung demonstrate certain peculiarities not observed in other types of pulmonary carcinomas.

They are often very slow in their growth, thus giving rise to a sense of false security on the part of the attending physician.

The cell type tends toward undifferentiation and, in women, a good percentage of carcinomas arising in this area are adenocarcinomas. In elderly men, squamous cell carcinomas in this position are not infrequent.

It has likewise been noted that carcinomas of the adeno type seen in this area are associated not infrequently with previous pulmonary scarring.

It is our desire to study this type of pulmonary tumor from the standpoint of its histology, of its association with scarring, and to further lend the study to the problem of growth.

In order that this may be accomplished, a relatively goodly series of tumors must be studied. It is our feeling that we have the material to carry out this work, using a relatively large series of cases at Harper Hospital and at Herman Kiefer Hospital, both of these institutions being located in Detroit.

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Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000

To carry forth this study, certain sums will be needed to cover the following items:

1. A secretary who has had certain clinical experience to aid in the evaluation of the charts.

2. The cost and upkeep of a work room at Harper Hospital, the room being furnished by the hospital, thus necessitating that the funds for research be used only in the maintenance of the room.

3. Supplies in the way of ordinary office supplies, including a typewrite.

Further aid will be needed in the evaluation of the X-rays by a Roentgenologist, a re-study of the slides on the pathologic specimens by a competent pathologist, and a resident in Thoracic Surgery who can aid in the evaluation of the charts and histories. These will be furnished without cost to the fund by the staff of Harper Hospital and in the person of a resident who is now on a research grant from Herman Kiefer Hospital.

It is felt that such a study will give us a new outlook on the so-called peripheral tumor. It may be of immense aid in evaluating the present treatment and the life history of such tumors. It is the desire that funds being allocated for this purpose be made to Harper Hospital, Detroit, Michigan, who will keep the books and return such amounts as are unused.

In view of the fact that such a study may take over a period of one year to complete, we are asking for a grant of $10,000.

6. Budget Plan:

a.	Salaries	$7,550.00
b.	Expendable Supplies	800.00
c.	Permanent Equipment	160.00
d.	Overhead (15% of a,b, e)	1,283.00
e.	Other	200.00
		$9,993.00

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7. Anticipated Duration of Work: ONE YEAR to EIGHTEEN MONTHS
(Budget shown is for the whole period)

8. Facilities and Staff Available: The Harper Hospital will furnish a room. The cooperation of a roentgenologist, a pathologist and of a resident in thoracic surgery will be furnished without cost by the Harper Hospital, for evaluation of charts and histories. A resident now being supported by a grant from Herman Kiefer Hospital will also be available without cost.

9. Additional Requirements: One typewriter, a secretary with special experience and training to aid in the evaluation of the charts. Ordinary office supplies, x-ray materials and upkeep of facilities and premises.

Signature WILLIAM M. TUTTLE, M. D.
Director of Project

A.R.W. CLIMIE
Business officer of the Institution
(for John R. McDonald M,D.
Director of Laboratories and Research
Harper Hospital)

Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000

PHYSIOLOGY of the RESPIRATORY SYSTEM #353

COMMITTEE:
Dr. Cattell, Chm.
Dr. Kotin
Dr. Jacobson
Dr. Rienhoff

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

APPLICATION FOR RESEARCH GRANT

Date: MAY 8, 1962

1. Name of Investigator: Charles W. La Belle, Ph.D.

2. Title: Assistant Professor of Environmental Hygiene

3. Institution & Address: Jefferson Medical College
1025 Walnut Street
Philadelphia, Pennsylvania

4. Project or Subject: EFFECT OF CIGARETTE SMOKE ON PULMONARY CLEARANCE

5. Detailed Plan of Procedure:

This laboratory has in the past devoted considerable attention to the investigation of those factors which determine the rate at which inhaled particles are eliminated from the lung. Starting with an early finding that weight for weight, small uranium dioxide particles are more toxic than large (La Belle, 1947); it was successively shown that the behavior of particulates is altered by the presence of adsorbable vapors (LaBelle, Long, and Christofano, 1955); that the clearance of particulates from the lung occurs in two stages, an early rapid phase being followed by a later slow phase (LaBelle et al.,1960); that the early rapid phase involves transfer of particles to the gastrointestinal tract (Brieger and La Belle, 1959); that the early rapid phase is characterized by the appearance of large numbers of histiocytes in the lung parenchyma (La Belle and Brieger, 1959); that the correlation between pulmonary clearance and the number of free motile phagocytes (as distinct from fixed tissue histiocytes) is extremely high ($p = 0.87$) (La Belle and Brieger, 1961); that the kinetics of the appearance and disappearance of these cells corresponds to the kinetics of pulmonary clearance (La Belle and Brieger, 1960); and finally, that the release of phagocytes can be artifically stimulated by administration of carbon particles in such a way as to accelerate the elimination of previously inhaled noxious particles (La Belle et al., 1962). Studies currently in progress involve assay of the biological properties of the carbon particles (La Belle and Bevilacqua, 1962), and the establishment of a routine therapeutic procedure for emergency treatment for inhaled radioactive particles (Bevilacqua and La Belle, unpublished).

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Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000

From these findings we conclude that early-phase pulmonary clearance is the biological function of these cells, and that conversely, the rate of clearance is determined by the number of phagocytes available. There is an opposing school of thought which believes that this early clearance process is caused by and controlled by the ciliated epithelium of the bronchial tree. For example, Dalhamn and his associates at the Karolinska Institute have shown that ciliary action is depressed by ammonia and formaldehyde (Dalhamn, 1956), by sulphur dioxide (Dalhamn and Rhodin, 1956), and by cigarette smoke (Dalhamn, 1959). Although Dalhamn questions whether all the effects of smog can be related to the blocking of the cilia by sulphur dioxide (Dalhamn and Strandberg, 1961), it remains the Swedish view that blocking or even slowing of the cilia will correspondingly inhibit pulmonary clearance.

If this view is correct, it follows that the correlation between lung cancer and smoking might derive from such blocking of the defenses against inhaled carcinogens. However, we do not accept this inference as correct, and we have the techniques and apparatus available to test the question esperimentally.

We have recently constructed in this labpratory an apparatus in which radioactive isotopes can be followed from organ to organ in intact rabbits. With this apparatus it is possible to determine in about a week a lung clearance curve which formerly required several months to construct by conventional methods of serial sacrifice and tissue analysis. This unit is designed to test animals in pairs, one rabbit being held as a control, the other being subjected to various trial therapies. It is proposed to use this same apparatus and technique to compare pairs of rabbits, with identical lung burdens of radioactivity, one of the pair being exposed to cigarette smoke. If the Swedish view is correct, clearance will be inhibited by the cigarette smoke; if we are correct, clearance will be unaltered or may even be slightly increased.

It has been found that about three weeks are required to accumulate enough replicate clearance curves to show practical differences between treatments with reasonable assurance; it is believed that about three months work would permit of adequate exploration of the various possibilities.

B I B L I O G R A P H Y

LaBelle, 1947: The variation of toxicity with particle-size of UO_2 dust. Federation Proceedings, 6, No. 1, March, 1947.

LaBelle, Long, and Christofano, 1955: Synergistic effects of aerosols: I. Particulates as carriers of toxic vapors. Arch. Ind. Health 11, 297-304. 1955.

LaBelle, Brieger, Goddard, Rastatter, and Zinger, 1960: Retention and effect of radioactive particulates in the lung. Am. Hyg. Jour., 21, 195-200, 1960.

Brieger and LaBelle, 1959: The fate of inhaled particulates in the early post-exposure period. Arch. Ind. Health 19, 510-515, 1959.

LaBelle and Brieger, 1959: Synergistic effects of aerosols. II. Effects on rate of clearance from the lung. Arch. Ind. Health 20, 100-105, 1959.

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LaBelle and Brieger, 1960: Basic physiologic mechanisms in the pulmonary response to inhaled particulates. Proceedings XIII International Congress on Occupational Health 1960.

LaBelle, Brieger and Vasso, 1962: Biological effects of carbon. Federation Proceedings, 21, No. 2, 1962.

LaBelle and Bevilacqua, 1962: Synergistic effects of aerosols. III. Carbon particles and air-borne ions. Amer. Ind. Hyg. Jour., (in press).

Bevilacqua and LaBelle, 1962: A proposed method for the therapeutic elimination of radioactive particles from the lung. Manuscript in preparation.

Dalhamn, 1956: Mucus flow and ciliary activity in the trachea of healthy rats and rats exposed to pulmonary irritant gas. Acta Physiologia Scand.; 36 supp. 123, pp. 1-161, 1956.

Dalhamn, and Rhodin, 1956: Mucus flow and ciliary activity in the trachea of rats exposed to pulmonary irritant gas. Brit. Jour. Ind. Med., 13, 110-113, 1956.

Dalhamn, 1959: The effect of cigarette smoke on ciliary activity in the upper respiratory tract. A.M.A. Arch. Otolaryngology 70, 166-168, 1959.

Dalhamn and Strandberg, 1961: The acute effect of sulphur dioxide on the rate of ciliary beat in the trachea of the rabbit, in vivo and in vitro, with studies of the absorptional capacity of the nasal cavity. Int. Jour. Air and Water Poll., 4, 154-167, 1961.

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6. Budget Plan:

a.	Salaries	$4,500.00
b.	Expendable Supplies	1,400.00
c.	Permanent Equipment	
d.	Overhead (15% of a,b, e)	915.00
e.	Other	200.00
	TOTAL	$7,015.00

BUDGET:

Salaries:		
	Principal Investigator	$2,500.00
	Assistant	1,500.00
	Part-time technician	500.00
	TOTAL SALARIES	$4,500.00
Expendable supplies:		
	Animals, isotopes, etc.	$1,400.00
Travel:		200.00
		6,100.00
	Overhead @ 15%	915.00
	TOTAL	7,015.00

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7. Anticipated Duration of Work: THREE MONTHS

8. Facilities and Staff Available: CHARLES W. LA BELLE - as principal investigator

D. M. BEVILACQUA - as assistant

Apparatus already built and operating.

9. Additional Requirements:

Summer salaries for principal investigator - and assistant, provision for part-time technician, animals, isotopes and travel.

10. Additional information (including relation of work to other projects and other sources of supply).

Grants from several sources have assisted development of techniques to their present state. No other agency will be involved in support of this project.

Signed CHARLES W. LA BELLE
Director of Project

1003542921

Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000

EPIDEMIOLOGY, STATISTICS and PSYCHOSOMATIC #354

COMMITTEE:
Dr. Wilson, Chm.
Dr. Cattell
Dr. Little
(Dr. Tagiuri)

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

APPLICATION FOR RESEARCH GRANT

Date: May 1, 1962

1. Name of Investigator: ELIHU KATZ, Ph.D.

2. Title: Associate Professor of Sociology

3. Institution & Address: The University of Chicago
1126 East 59th Street
Chicago 37, Illinois

4. Project or Subject: SOCIAL AND PSYCHOLOGICAL CONSTRAINTS ON THE TRANSLATION OF MOTIVES INTO ACTION: THE CASE OF CIGARETTE SMOKING.

5. Detailed Plan of Procedure:

Some time ago, I worked out a design for research on decision-making with respect to personal smoking behavior. I was particularly interested in the fact that the widespread circulation of information concerning the possible link between smoking and lung cancer seemed, in the aggregate, to have little effect. As in the case of any communication "campaign", this could be because people were uninformed, or unbelieving, or unmotivated, or unable to translate their motivation into action. There is an implicit typology here that can be formulated as follows:

	Heard?	Believe?	Should Quit?	Quit?
Uninformed	No	No	No	No
Unbelieving	Yes	No	No	No
Unmotivated	Yes	Yes	No	No
Unable	Yes	Yes	Yes	No
Quit	Yes	Yes	Yes	Yes

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Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000

I was interested in portraying the different kinds of people who fall into the several categories and, particularly, in characterizing their interpersonal environments (attitudes of their doctors, their spouses, their friends, etc.) The design, basically, called for (1) a large-scale screening survey to locate an adequate number of respondents of each type (2) intensive interviews with respondents located in this way, and (3) brief (perhaps telephone) interviews with their closest associates.

For several reasons, I have had to put this plan aside. Indeed, I would not now have recalled it if it were not for the fact that a graduate student in our Department has approached me with a proposal to write a term paper, hopefully leading to a Master's essay, on a closely related topic. My impression of this student, Mr. Bruce Straits, is favorable; he shows evidence of being interested and capable.

I am writing, therefore, to request support for one summer's work by Mr. Straits, under my supervision, to conduct a small pilot study within the framework of my overall design. I would want to focus particularly on the comparison of those who thought they should stop smoking but did not (or could not), and those who thought so and did. From a theoretical point of view, the study would be concerned with the conditions favoring or disfavoring the translation of motives into action, as well as the conditions associated with the management and toleration of "dissonance" between ideas and behavior. In general, I would hope that a number of insights might result relating to public perception of the gratification and disadvantages of smoking.

I am thinking in terms of 25-50 interviews with each group which, in turn, would require a considerably larger number of "screening" interviews. It may be possible to do the screening by means of the addition of a "rider" question in a local survey. I believe that Mr. Straits can do most of the interviewing with some assistance from another graduate student. I am requesting summer salary for Mr. Straits, additional funds for another interviewer and/or the "rider" question, plus the expenses of clerical help and supplies.

If the results of this work are promising, I would hope to be able to continue it in the future.

6. Budget Plan:

a.	Salaries	$1,500.00
b.	Expendable Supplies	250.00
c.	Permanent Equipment	--
d.	Overhead (15% of a,b, e)	337.50
e.	Other	500.00
	TOTAL	2,587.50

7. Anticipated Duration of Work: 6 Months

8. Facilities and Staff Available: As outlined above

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R: REDACTED MATERIAL

9. Additional Requirements:

10. Additional Information (Including relation of work to other projects and other sources of supply)

The area of communication research has been of continuing interest to me. In the last few years, I have been giving particular attention to problems of the diffusion and acceptance of innovation. I am currently at work on a book-length manuscript on this subject, attempting to integrate a large number of relevant studies stemming from a variety of research traditions. I am enclosing a copy of my list of publications.

Signature ELIHU KATZ
Director of Project

W. B. HARRELL
Vice President for Business Affairs

BIOGRAPHY OF PRINCIPAL INVESTIGATOR

10035A2924

Name: ELIHU KATZ

Born: REDACTED REDACTED

Education:
B.A., Columbia College, Columbia University (1948)
M.A., Dept. of Sociology, Columbia University (1950)
Ph.D., Dept. of Sociology, Columbia University (1956)
Certificate, Japanese Language and Area Program, Army Specialized Training Program, University of Chicago (1946)

Academic Employment:
Research Associate, Bureau of Applied Social Research, Columbia University, 1951-54.
Lecturer, Department of Sociology, School of General Studies, Columbia University, 1952-54.
Visiting Lecturer, Dept. of Sociology, Eliezer Kaplan School of Economics and Social Science, The Hebrew University, 1956-58.
Assistant Professor, Associate Professor, Dept. of Sociology and The College, University of Chicago, 1954-present (on leave of absence: 1956-58).

Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000

Publications:

1. (with Paul F. Lazarsfeld) Personal Influence: The Part Played by People in the Flow of Mass Communication, Glencoe: The Free Press, 1956.

2. (with Herbert Menzel) "Social Relations and Innovation in the Medical Profession: The Epidemiology of a New Drug," Public Opinion Quarterly XIX, 4, Winter 1955-56, pp. 337-352. (Reprinted in Maccoby, Newcomb and Hartley, eds., Readings in Social Psychology, 3rd edition; and Jaco, ed., Patients, Physicians and Illness.

3. (with P. M. Blau, M. L. Brown, F.L. Strodtbeck) "Leadership Stability and Social Change: An Experiment with Small Groups," Sociometry, XX, 1, March, 1957, pp. 36-50.

4. "The Two-Step Flow of Communication: An Up-to-Date Report on a Hypothesis," Public Opinion Quarterly, XXI, 1, Spring, 1957, pp. 61-78. (Reprinted in Schramm, ed., Mass Communication, (2nd ed.); and in Walters, Snider and Sweet, eds., Readings in Marketing).

5. (with Rolf B. Meyersohn), "Notes on a Natural History of Fads," American Journal of Sociology, LXXX, 6, May, 1957, pp. 594-601. (Reprinted in Larrabee and Meyersohn, eds., Mass Leisure; and in Kelley and Lazer, eds., Managerial Marketing.)

6. (with John Johnstone) "Youth and Popular Music: A Study in the Sociology of Taste," American Journal of Sociology, LXII, May, 1957, pp.563-568.

7. (with James Coleman and Herbert Menzel) "The Diffusion of an Innovation Among Physicians," Sociometry, XX, No. 4, December, 1957, pp. 253-270.

8. (with James Coleman and Herbert Menzel), "Social Processes in Physicians' Adoption of a New Drug," Journal of Chronic Diseases, IX, 1, January, 1959, pp. 1-19.

9. (with Herbert Menzel and James Coleman), "Dimensions of Being 'Modern' in Medical Practice," Journal of Chronic Diseases, IX, 9, January, 1959, pp. 20-40.

10. (with Awraham Zloczower), "Ethnic Continuity in the Second Generation," Megamot, (Hebrew), IX, 3, July 1958, pp. 187-200.

11. "Mass Media Research and the Study of Popular Culture," Studies in Public Communication #2, Summer 1959, 1-6.

12. "Communication Research and the Image of Society: On the Convergence of Two Traditions," American Journal of Sociology, LXV, 5, March 1960, pp. 435-440.

13. (with S.N. Eisenstadt), "Observations on the Responses of Israeli Organization to New Immigrants," Administrative Science Quarterly, V, 1, June 1960, 113-133.

14. (with K. Kessin, J. McCoy, L. Pinto, R. Strieby), "Public Reaction to the Unscheduled Sounding of Air-Raid Sirens in a Metropolis: A First Glance at the Data," in Baker and Rohrer, eds., Symposium on Human Problems in the Utilization of Fallout Shelters, Washington, D.C.: Disaster Research Group, National Academy of Sciences-National Research Council, 1960.

10035425

Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000

Publications:

15. Joy in Mudville: Public Reaction to the Surprise Sounding of Chicago's Air Raid Sirens, Report #75, National Opinion Research Center, June 1960. (also see: "The Night the Sirens Wailed in Chicago," Sunday magazine section, Chicago Sun-Times, April 24, 1960).

16. Contribution to "Jewishness and the Younger Intellectuals: A Symposium," Commentary, April 1961.

17. "The Social Itinerary of Technical Change, "Human Organization, XX, 2, Summer 1961, 70-82.

18. (with Awraham Zloczower) "Ethnic Continuity in an Israeli Town, I. Relations with Parents," Human Relations, XIV, 4, 1961, pp. 293-308.

19. (with Awraham Zloczower) "Ethnic Continuity in an Israeli Town, II. Relations with Peers," Human Relations, XIV, 4, 1961, pp. 309-327.

20. "Notes on the Unit of Adoption in Diffusion Research, "Sociological Inquiry, Vol. XXXII, Winter 1962, No. 1.

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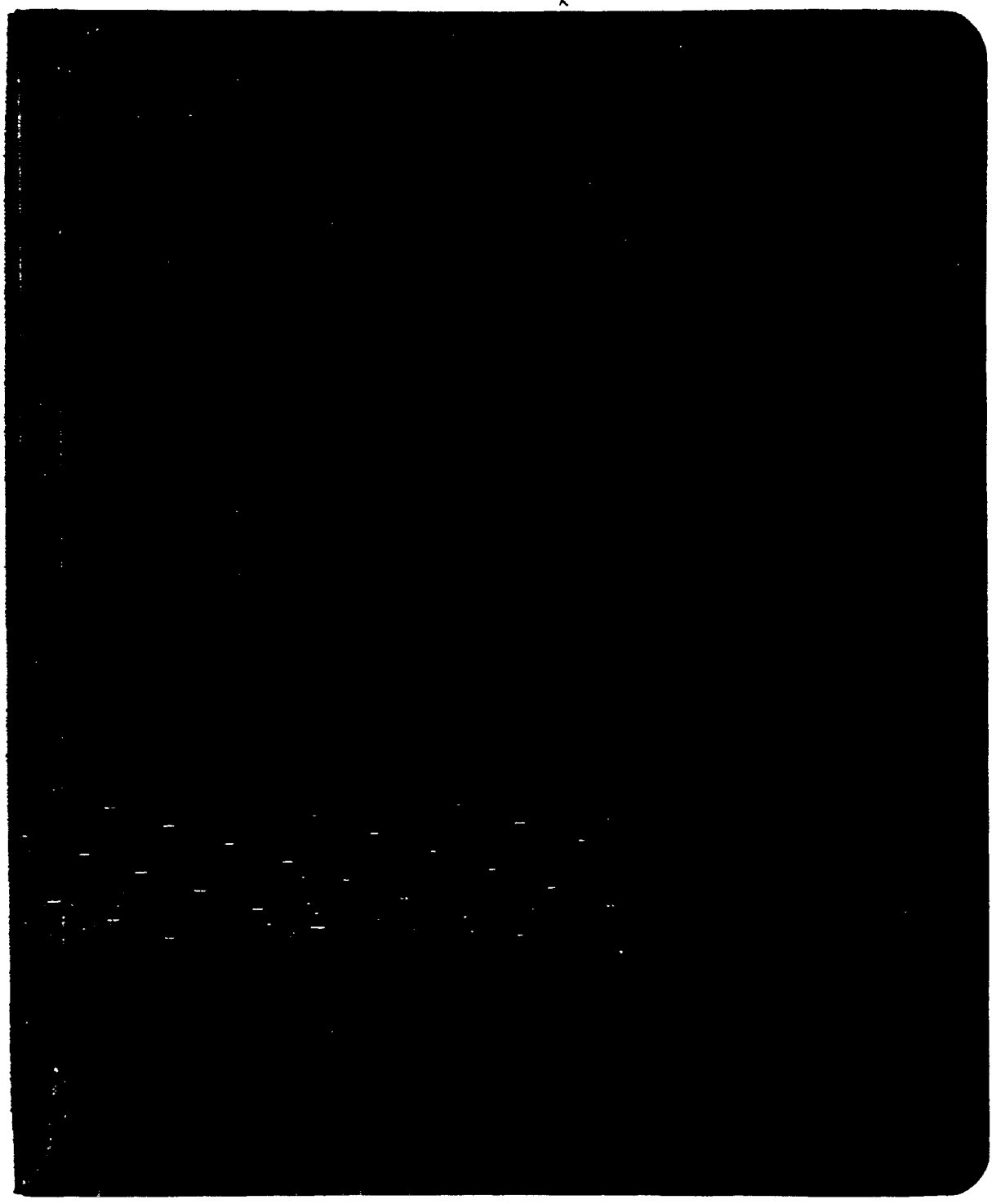
Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000



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Source: https://www.industrydocuments.ucsf.edu/docs/srvm0000